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TREATMENT OF DIABETIC COMA

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DIABETIC coma is the unique complication of diabetes, resulting from insulin deficiency and failure of diabetic control. Although the name implies unconsciousness, patients with diabetic acidosis are in grave danger long before unconsciousness appears, and, therefore, the term, coma, may be properly applied to early as well as late stages of diabetic ketosis. The disturbance in carbohydrate, protein, and fat metabolism resulting from insulin deficiency has many aspects. Primarily, however, it is the failure of carbonhydrate metabolism which results in excessive oxidation of fat and consequent increased production of the ketone bodies which characterizes diabetic coma. It is (1) always an emergency, (2) always remediable if diagnosis is made early and sufficient treatment is given, and (3) preventable.

Incidence.—At one time, diabetic coma was the chief cause of death and the almost inevitable culmination of a diabetic patient's history. Before the discovery of insulin, it was rare that a diabetic child lived more than two years. Actually coma caused the death of three-fifths of all patients dying in the Naunyn period before the introduction of the undernutrition treatment by Frederick Allen. During the Allen era (1914-1922) mortality fell to 41 per cent. With

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the introduction of insulin—the beginning of the Banting era—diabetic coma was successfully treated; and today no one needs to die of diabetic coma unless complications in themselves fatal are present.

Historic.—Prior to 1857, there had been references to the winelike odor of the breath in severe forms of diabetes. The first allusion to the polyuria of diabetes mellitus is found in the papyrus Ebers, discovered in 1872 at Luxor in Egypt, which is from about 1500 B.C. About the sixth century A.D., Indian doctors mention in ancient Sanskrit texts somnolence, and difficulty in breathing strongly suggestive of ketosis. W. Prout[1] recognized the comatose state as a complication of diabetes. In 1857 Petters[2] identified acetone in the breath, blood, and urine and developed a theory that acetone was the cause of diabetic coma. It was soon found, when acetone tests became available in the clinic, that acetonuria might occur in other conditions besides diabetes.

In 1850 the French writer, Boussingault, developed a method for the estimation of ammonia in the urine. The highest percentage of ammonia in the urine was found in the sample of elephant's urine. The next highest was found in the urine of a woman who had diabetes.

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In 1868 Gerhardt recorded the fact that the urine of patients with severe diabetes gave a color reaction with ferric chloride, a test we now recognize as identifying acetoacetic acid. The famous description by Kussmaul,[3] in 1874, emphasized the contrast between the powerful respiratory movements and the extreme weakness of the patient.

Friedrich Walter, in 1877, published the results of careful experiments with animals. Administering acid to these animals, he showed clearly the sequence of symptoms—anorexia, weakness, rapid respiration, coma, and death—which resulted. In animals receiving a lethal amount of hydrochloric acid, the carbon dioxide of the blood fell to 2.07 volumes per cent. He clearly appreciated that the quantity of carbon dioxide in the blood was essentially in proportion to the quantity of alkali contained in the blood.

Minkowski showed that the excessive amount of acid found in the urine was beta hydroxybutyric. Magnus Levy showed that it was the levorotatory form and developed an optical method for its estimation. Stadelmann,[4] using Walter's experiments, in 1883 founded the theory of acid poisoning as the cause of coma and increased ammonia excretion in diabetes. He inaugurated the treatment of acidosis by means of alkali.

Thus, before 1890, the three important ketone bodies—acetone, diacetic acid, and beta hydroxybutyric acid—had been identified.

Naunyn recognized the tremendous loss of alkali and repeatedly referred to the condition as alkalipenia. In the 1890's, acetonuria even in normals was relieved by carbohydrate feeding. In 1900 the part played by the liver became clearer, especially the fact that excessive ketone bodies (acetone, CH_3-CO-CH_3; diacetic acid, CH_3-CO-CH_2-COOH; and β-hydroxybutyric acid, CH_3-CHOH-CH_2-COOH) were formed from fat in the liver. "Fat burns in the fire of carbohydrate, but without carbohydrate it smokes," said Woodyatt in 1916.

Forsner, by forcing feeding of fat, produced excretion of 42.8 Gm. "ketone bodies" in one day. The theory of electric dissociation developed out of the work of Svante Arrhenius and Vant'Hoff at the turn of the century. It is sometimes forgotten, although the blood is said to be neutral with a pH of 7.4, that actually red litmus paper turns blue in the blood. In 1916, L. J. Henderson of Harvard changed the terminology, and "acidosis" was applied to the lowering of the alkaline reserve.

The studies of antiketogenesis in this country initiated by Rollin Woodyatt dominated the field at the time that the discovery of insulin came about. Following the discovery of insulin, attention was centered on the extraordinary alterations in carbohydrate, protein, and fat metabolism and suppression of the excess ketone formation in the liver which followed its use in diabetic coma. In the last ten years, attention has been concentrated upon the dehydration and losses of electrolyte, especially potassium, and consideration of the best methods for repair of these losses.

Today, the chief points of issue in the treatment of diabetic coma are related to insulin dosage, the value of the early administration of glucose and the necessity for giving additional potassium, magnesium, and phosphate.

TABLE I. DIABETIC COMA, 864 CASES (643 PATIENTS) (JOSLIN CLINIC)

CASES (NO.) DATES	AGE (AVERAGE)	D.M.* (YR.)	BLOOD		INSULIN (UNITS)	FATAL (PER CENT)
			SUGAR	CO_2 (MM.)		
52 (1923–26)	31	3	480	6	161	18
411 (1927–39)	30	4	501	5	208	11
341 (1940–50)	29	7	536	6	302†	3
60 (1951–53)	30	7	511	6	344†	5

*D.M. = Diabetes mellitus.
†In addition, 20 to 420 (average 72) units given 215 patients prior to admission on phone order.

Treatment Today.—During the past thirty years, 864 instances of diabetic coma (in 643 patients) have been treated at the New England Deaconess Hospital (Table I). We use the word diabetic coma for those patients with diabetic ketosis in whom the carbon dioxide of the blood plasma is 9 meq. per liter (21 volumes per cent) or less. This arbitrary selection of patients recognizes that patients may be critically ill before this level of carbon dioxide is reached. The reason for this selection of patients is a clinical one. Prior to the use of insulin, practically no patients with diabetic coma recovered if the carbon dioxide of the blood plasma was below 20 volumes per cent, whereas it was not uncommon for the treatment of those days to result in recovery in patients with higher values. In this series, however, are included patients who, without the aid of insulin, would have died. These 864 episodes of coma occurred in 643 patients

whose ages ranged from 11 months to 77.5 years of age. Of these, 414 were females and 229 were males, a disparity between the sexes quite unexplained by the relative incidence of the disease in women and men. Somewhat less than one-third of the cases were under 15 years of age, and in this age group diabetes is fully as common in males as in females. A striking fact is that the average age of patients with diabetic coma has remained almost constant throughout these thirty years. Extremes of age do occur; and actually in babies diabetes is usually discovered only when the child is in acidosis.

The first striking feature of the series is the changing duration of diabetes prior to coma. In the earlier years, patients had had diabetes an average of only three to four years; but in the last twelve to thirteen years, the average duration of diabetes prior to coma has risen to seven years. This change may be attributed to a number of factors, which include: (1) the more frequent diagnosis of diabetes before coma through diabetic detection drives; (2) the wider education of patients in the use of insulin, diet, and urine-testing to control their disease; (3) the improvement in treatment of ketosis; (4) and the discovery of the antibiotics which have cured diabetics of the severe infections to which they are particularly prone. A further striking feature is the fact that the average blood sugar and carbon dioxide level seen in coma have remained fairly constant. It is evident that, over the years, the severity of acidosis has been about the same, and the improved results seem, therefore, more clearly attributable to improvements in treatment. Indeed, we feel sure that the change indicated in insulin dosage (Table I) is the most important cause of the decline in the death rate. Thus, in the earlier period only 161 units were given in the first twenty-four hours; but, in the last ten to fifteen years, the average amount of insulin given in the first twenty-four hours has been more than 300 units. Indeed, 344 units, the average during the last two years for 60 cases, is the highest amount yet given. Even this figure is less than the actual amount because, in these recent years, more and more frequently we have ordered insulin given to the patient in the ambulance before admission to the hospital. Our feeling is that the insulin given in the two or three hours prior to admission has, in many cases, been a most important element in preventing the development of insulin resistance and a graver condition upon arrival.

The death rate has fallen from 18 per cent in the early years to only 3 per cent in the 341 instances of coma treated between 1940 and 1951. In the two years ending in 1953, 3 deaths from anuria, hypopotassemia, and pulmonary edema have raised the average to 5 per cent. If one takes the period from 1940 to 1953, the death rate percentage is 3.5. We hardly expect that this percentage will fall in any considerable series of patients because, with the increasing average duration of diabetes, diabetic coma will be complicated more and more frequently by fatal factors such as coronary occlusion and the uremia of the diabetic nephropathy.

Insulin.—A patient developing or actually in diabetic coma needs insulin immediately. The first consideration, therefore, even before the patient arrives at the hospital, is the dosage to be given. When information making certain

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the diagnosis of coma is given over the telephone, insulin in dosage varying from 20 to 50 or even 100 units can usually be given safely. Actually, any patient in diabetic coma deserves treatment in a hospital. As soon as plans for the patient's admission are known, preparations for his arrival and treatment should be made.

Hot-water bottles, blankets, stomach and rectal tubes, salt and glucose solution, insulin, and stimulants should be assembled. A special coma cart with these materials has proved of great use in many hospitals.

Before giving insulin, the first step is the diagnosis. The differential diagnosis must first of all exclude the possibility that the patient's unconscious state is already due to overdosage of insulin. Therefore, no insulin is ever given to a drowsy or unconscious diabetic patient without evidence from the urine or blood sugar test that the patient is in need of it.

TABLE II. COMA, 213 CASES, 1946-1953

BLOOD SUGAR ON ADMISSION	CASES (NO.)	AVG. INSULIN 1ST 3 HOURS (UNITS)	AVG. INSULIN 1ST 24 HOURS (UNITS)
1,300–1,600	3	883	1,683
1,000–1,300	13	514	825
600–1,000	65	335	526
400–600	69	209	329
200–400	60	99	151
100–200*	3	71	140

*Low values due to insulin given en route to hospital.

In Table II is summarized the insulin dosage (regular and not protamine insulin) in the first three and the first twenty-four hours, respectively, of 213 cases of coma treated at the Deaconess Hospital between 1946 and 1953. The proper goal is to ascertain as nearly as possible the patient's total insulin requirement and to administer this dose as soon after the diagnosis as possible. Often one cannot predict the insulin requirement until the second blood sugar test is available to demonstrate the degree of effectiveness of the first dose. In many patients, the initial dose of insulin may be only 40 or 50 units, particularly in children or young patients with diabetes of short duration. For adults, larger doses are needed. In severe cases, especially those with circulatory collapse, half the insulin dose is usually given intravenously. It will be seen from Table II that the insulin given in the first three hours after admission to the hospital has actually been about 50 or 60 per cent of the total amount required in the first twenty-four hours. Our feeling at present is that unless at least 50 per cent of the total amount required to re-establish normal metabolism is given in the first three hours, the speed of insulin administration has been too slow. The urgency of giving large doses of insulin in the first three hours rests upon the necessity of controlling polyuria, glycosuria, and hyperglycemia. The excessive hyperosmolarity of the blood due to the excessive concentration of glucose exerts tremendous osmotic force, causing withdrawal of water from cells and conse-

quent intracellular dehydration. The more rapidly the concentration of glucose can be reduced, the more rapidly will intracellular rehydration proceed. Our custom usually is to give insulin in divided doses at frequent intervals, sometimes as often as once in fifteen to thirty minutes. In the more severely ill patients with circulatory collapse, insulin is commonly given intravenously, occasionally into the jugular vein.

In Table III is summarized an outline of the treatment of diabetic coma which has been developed over the years at the New England Deaconess Hospital. This serves as a summary of our present practice and as a guide in the treatment of cases. This outline emphasizes the importance of rapid decision, and treatment hour by hour. Thus, in the first hour after admission, necessary laboratory data are obtained. The patient is catheterized. The urine is examined for sugar, acetone, diacetic acid, albumin, coma casts,[5] and pyuria. The presence of many casts, hyaline and granular, in the urine sediment, often described as a "shower," has been frequently described since the time of Külz. The casts occur frequently (even in children) with severe ketonuria long before unconsciousness exists. Blood chemical examinations are obtained. The patient is examined for complications and to establish surely the diagnosis of diabetic coma as against meningitis, cerebral hemorrhage, and uremia. In the second to sixth hours, the endeavor is to control the diabetes and to bring the gastrointestinal tract into a state where the taking of food may be begun. During the sixth to the twenty-fourth hours, the administration of food such as oatmeal gruel, orange juice, or milk is begun in those patients with the less severe type. Obviously, in patients remaining unconscious for more than twenty-four hours, intravenous alimentation only is possible.

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TABLE III. TREATMENT OF DIABETIC COMA

(Joslin Clinic, New England Deaconess Hospital, November, 1954)

FIRST HOUR AFTER ADMISSION: Special nurse, preferably experienced in coma treatment, for the first few hours.

Laboratory:

1. *Urine.* Examine for sugar, acetone, diacetic acid, albumin, coma casts, and pyuria. Catheterize if necessary.
2. *Blood.* Test for sugar, CO_2 content, and nonprotein nitrogen, with emergency report inside the hour. White blood count.

Clinical:

3. *Search for complications and establish diagnosis.*
   - A. History to explain cause of coma.
   - B. Physical examination, noting particularly—
     - (a) State of consciousness, type of respiration, pulse rate, blood pressure, and rectal temperature.
     - (b) Look for soft eyeballs, dry tongue, dilated stomach, cold and mottled skin, and impacted rectum.
   - C. X-ray chest and abdomen when possible.
   - D. ECG (a) coronary (b) potassium changes.
4. *Insulin.* 50 to 100 units of regular insulin subcutaneously at once for adults. In severe cases, especially with circulatory collapse, give insulin intravenously. If blood sugar exceeds 300 mg. per 100 c.c. and if the blood CO_2 content is 9 millimols per liter (20 volumes per cent) or less, the dose will need to be repeated. The insulin dose would

TABLE III—CONT'D

be proportionately less (20 to 40 units) in young children, especially if diabetes is of recent onset. In cases with blood sugar between 600 and 1,000 mg., give 200 units additional, and with blood sugar over 1,000 mg., give 300 units additional.

5. *Gastric Lavage.* Use large tube, aspirate completely and wash stomach with warm water with greatest care.
6. Normal saline intravenously, 2,000 c.c. It is desirable to change to a solution of saline lactate after the first liter of saline solution is given (to 700 c.c. saline add 1 ampoule [40 c.c.] 1 molar lactate and make up to 1,000 c.c. with sterile distilled water). If lactate is unavailable, normal salt solution may be continued. Avoid too rapid administration, especially in older patients.
7. Keep patient warm yet avoid burns, as from hot-water bottle.
8. Give no potassium solutions by mouth or by vein (a) when oliguria is present or impending (b) unless blood analysis or ECG clearly indicate hypokalemia (c) as a rule until after 12 hours of treatment.

SECOND TO SIXTH HOUR: The gravity of the case may require repetition of first hour's total insulin in the second hour.

9. Repeat blood sugar and CO_2 determinations after three hours. For rising blood sugar give insulin hourly 50 to 200 units or more, according to physician's judgment of prognosis.
10. Fluids by mouth (as soon as tolerated), limited to 100 to 120 c.c. per hour of broth, ginger ale, orange juice, tea, or coffee, to be sipped by patient or spooned by nurse. For children limit to 50 c.c. per hour at first. Then, if nausea and vomiting recur, withhold fluids orally for 12 hours (lavage stomach again if indicated) and then resume.
11. *Enema* for cleansing and to relieve abdominal distension.
12. Record and note changes in blood pressure, pulse, and temperature hourly. Consider transfusion if in deep shock.
13. Urinalysis for sugar and diacetic acid every hour. Record hourly output as index of dehydration and renal function.
14. Antibiotics (parenteral) penicillin, streptomycin or Aureomycin frequently needed.

SIXTH TO TWENTY-FOURTH HOUR:

15. Repeat blood sugar and CO_2 determinations. Give insulin 50 to 200 units if blood sugar and CO_2 levels are not improving. Insulin (regular) may be given according to urine tests every 1 to 4 hours if fall in blood sugar has been satisfactory.

If test is—	Red	Orange	Yellow	Green	Blue	
Give—	20	16	12	0	0	units

For young children give half dose.

16. Soft or liquid food such as oatmeal gruel, orange juice, or milk diluted half and half with lime water, not to exceed 10 Gm. carbohydrate per hour. Glucose (5% in saline) I.V. only when blood sugar approaches normal.
17. *Urinary output.* Observe this closely and note with alarm any sign of oliguria. Treat with 1,500 c.c. intravenous saline if shock is persisting. Repeat as necessary. For anuria, associated with hypochloremia, give 50 c.c. of 10 per cent salt solution intravenously. Never give hypertonic glucose solution to promote diuresis. Beware producing excessive diuresis with consequent loss of base, especially of potassium.
18. Sudden onset of muscular weakness and shallow respiration suggest hypokalemia. Potassium may be given p.o. or i.v., if changes in ECG or in serum potassium are present. (See below.)

SECOND DAY AND SUCCEEDING DAYS:

19. Soft food. Diet: carbohydrate 100 to 150 Gm., protein 50 Gm., fat 50 Gm. Gradually return to standard diabetic diet for age and weight with carbohydrate 150 to 200 Gm., protein 60 to 100 Gm., fat 60 to 120 Gm. daily.

TABLE III—CONCLUDED

ADDITIONAL NOTES

I. Differential diagnosis should include the acidosis of diabetic nephropathy in patients with diabetes of long duration. Uremia may result in retention of ketone bodies in the blood plasma, although they may be absent or reduced in concentration in the urine. Examine plasma for acetone by nitroprusside test* or quantitate ketone bodies in blood.

Total Ketones in Blood

	mg. per 100 c.c.
Normal	0 to 5
Nondiabetic uremia	5 to 60
Diabetic coma	50 to 200+

II. To avoid pulmonary edema, rarely exceed 5,000 c.c. parenteral fluid in 24 hours and check frequently for signs of edema. If urinary output exceeds 40 c.c. per hour after parenteral fluid has been given up to 3,000 c.c., grave dehydration no longer exists.

III. Electrolyte-containing solutions: If serum K or electrocardiogram indicates need, 40 meq.K may be added to the intravenous solution. Potassium should not be given intravenously in excess of 25 meq. per hour!! Rarely is it wise to exceed 80 meq. in 12 hours unless definite hypopotassemia is present and urine secretion is ample. After 12 to 24 hours if 3 to 4 Gm. potassium cannot be taken by the patient in diabetic diet, a simple solution may be taken in divided amounts. Thus, 200 c.c. orange juice plus 2 Gm. potassium phosphate may be diluted with water to 500 c.c. Of this give 100 c.c. per hour. With fall in blood sugar and need for potassium, a 5 c.c. ampule (2 Gm. dibasic potassium phosphate and 0.4 Gm. monobasic potassium phosphate) may be added to 1,000 c.c. of 5 per cent glucose for intravenous administration if indicated.

IV. Electrocardiographic signs of

A. Low serum potassium (below 3.0 meq.).
1. Lowered T waves.
2. Depressed ST segments.
3. Lengthened QT, or appearance of U wave.

B. High serum potassium (above 6.0 meq.).
1. High, peaked T waves.
2. Wide QRS
3. Disappearance of P waves.
4. Final disorganization of ECG.

Note: A normal ECG does not exclude K deficiency.

*Plasma Acetone Test: 4 c.c. of blood in an oxalate tube centrifuged until clear plasma obtained. Make solutions of 1 in 2, 1 in 4, and 1 in 8 with normal saline or tap water. Place 3 drops of undiluted plasma and the three dilutions on separate small mounds of acetone test powder. Depth of purple color indicates concentration of acetone and in some cases may be used as a clue to insulin resistance.

The clear relation between the insulin requirement and the level of the blood sugar is seen in Table II.

The importance of the blood sugar level rests upon several facts. The hyperglycemia is due to breakdown of intracellular glycogen and protein, and nonutilization of glucose by the body cells. As long as severe hyperglycemia is present, these cells do not have a normal metabolism. Furthermore, hyperglycemia represents excess osmolarity of the extracellular fluid, with consequent dehydration of the cells. Reduction of the blood sugar, therefore, promotes cellular rehydration as well as normal intracellular metabolism.

Fluids.—The excessive dehydration, one of the most important features of diabetic coma, is evident in the dry and inelastic skin, the dryness of the tongue and mucous membranes of the mouth, and the soft eyeballs. Soon after insulin

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was introduced, it was evident that in advanced diabetic coma the dehydration and starvation produced losses of electrolytes which exceeded the catabolism of the tissue represented by the nitrogen excretion. The chief aim in the treatment of diabetic coma with insulin and fluid is to make possible the restoration of normal feeding as soon as possible. Although normal salt solution has proved an effective method of rehydration in the great majority of coma cases, in patients profoundly comatose, in shock and with acidosis of long duration, the use of special fluids is clearly indicated.

A patient in coma has lost mainly intracellular but also extracellular water and electrolytes. The main electrolytes lost from the extracellular fluid are sodium and potassium. The main electrolytes lost from the intracellular fluid are potassium and phosphate.

As we have seen, when coma develops, a high level of ketoacids appears in the plasma. Since the kidney will not excrete a urine with a pH lower than 4.8, a sizable percentage of these acids must be excreted in combination with base. Normally, the kidney conserves the so-called "fixed body bases" by the substitution of ammonia and hydrogen ions, manufactured in the renal tubular cells, for sodium and potassium. However, in the presence of diabetic acidosis, the production of ammonia and hydrogen by the tubules is impaired, and, therefore, in order to keep urine pH at 4.8, sodium and potassium are lost in large amounts in the urine. The loss of sodium results in a disturbance in the sodium:chloride ratio in the extracellular fluid. This ratio is normally 1.3 (150 meq. of sodium to 120 meq. of chloride per liter of plasma water). In coma cases, although the actual concentration of sodium may be normal due to loss of water, there is relative retention of chloride, resulting in hyperchloremia, a reduction in the sodium:chloride ratio from 1.3 to about 1, and aggravation of the existing acidosis. This seems to occur even in patients who have lost a great deal of chloride through vomiting.

Glucose, particularly at high levels, as in these coma patients, is an osmotic diuretic, and huge amounts of water are lost from the extracellular spaces of these patients. A normal 70 kg. man has an extracellular fluid volume of about 14 liters. At the height of acidosis, this may be reduced to 6 or 7 liters. Despite this tremendous loss of water and sodium, the extracellular fluid is hypertonic because of the presence of glucose, ketoacids, and excess chloride. Because of the law of osmotic equilibrium, this hypertonicity of the extracellular fluid causes water to leave the cells and results in intracellular dehydration. Breakdown of cell solids releases potassium and phosphate, which are excreted in the urine.

The objects of fluid therapy, then, are (1) to correct the hyperchloremia and hyperosmolarity of the patient's extracellular fluid, (2) to provide sodium, chloride, and water to expand the extracellular fluid volume, (3) to correct intracellular dehydration, and, finally, (4) to provide potassium and phosphate necessary for the restoration of stores of intracellular glycogen and protein.

The ideal initial replacement fluid, then, contains sodium in excess of chloride, and water in excess of sodium—that is, a slightly hypotonic solution of a mixture of sodium chloride and sodium lactate. Normal saline may also

be given, to restore the volume of the extracellular fluid. If the pH, electrolyte, and water content of the extracellular fluid are restored, and the patient receives adequate fluid, intracellular dehydration will soon be corrected. The restoration of adequate potassium and phosphate is best accomplished by the diet, since the intravenous administration of potassium in patients with poor renal function may lead to hyperpotassemia. In an occasional patient, the rapid expansion of the extracellular fluid with sodium chloride may result in precipitous drop in serum potassium and the development of clinical and electrocardiographic abnormalities. The development of weakness or paralysis in a patient otherwise responding well to therapy demands a rapid determination of serum K or an electrocardiogram, where flattening of the T waves and a prolonged Q-T interval are indicative of hypopotassemia. In these patients 40 to 50 meq. of potassium acetate may be added to a liter of saline, and the liter infused over a period of three to four hours. This may be repeated in twenty-four hours if necessary.

The measurement of dehydration is difficult. It is important to give enough fluid and yet to avoid excessive amounts. In general, one can say that a patient who is excreting 40 c.c. of urine per hour after parenteral fluid is no longer seriously dehydrated.

Hypertonic solutions should never be given to these patients. A 10 per cent solution of dextrose contains 556 milliosmols per liter, as compared to a normal body water osmolarity of 320, and will only aggravate the existing intracellular dehydration.

Gastric lavage should be carried out routinely in any patient who is in serious acidosis. The dilated stomach of patients with diabetic coma is well known, and the danger of aspirating fluid and producing pulmonary damage has been proved frequently at autopsy. The main purpose of the gastric lavage and the enema, however, is to prepare the intestinal tract for the taking of food which would include not merely water and glucose but protein, fat, minerals, and vitamins.

Circulatory stimulants are practically never needed with children and in adults rarely produce any startling effects. Norepinephrine may be given intravenously for extreme collapse, but beware of extravasation and resulting gangrene.

Blood transfusions have been used rarely in our patients but might be indicated in severe shock. It must not be forgotten that in older diabetic patients who may have coronary arteriosclerosis, the rapid increase in blood volume by the use of plasma or whole blood has more than once produced pulmonary edema or cardiac failure.

Glucose-containing solutions are no longer given in the first hours of the treatment of diabetic coma. No one would argue that the administration of 5 or 10 Gm. of glucose intravenously, or the giving of glucose after the first six to ten hours when the acute condition had been overcome, will be harmful. The plea is against the common practice of giving much larger amounts of glucose from the very beginning of treatment, as if the administration of glucose was itself an essential part of the treatment of coma. Glucose itself is entirely inert until it is phosphorylated through the action of insulin. In diabetic coma the amount

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of excess glucose unutilized in the blood and the extracellular fluid in a patient of 70 kg. weight with a blood sugar of 700 mg. per 100 c.c. may be calculated as follows:

	Diabetic Coma	*Normal*
Blood sugar	700 mg.	100 mg.
Glucose in blood and extracellular fluid	98 Gm.	14 Gm.

Assuming 20 per cent of body weight to be blood and extracellular fluid, there is thus an excess of 84 Gm. of glucose which is unutilized. Because of the block due to insulin deficiency, the addition of more glucose will not make this glucose any more useful. The action of insulin is (1) to facilitate the transformation of glucose to glycogen; (2) to increase the ability of the patient to oxidize glucose to carbon dioxide and water; (3) greatly to favor the transformation of glucose to fat.[6,8] Observations of the oxygen consumption during diabetic coma in 6 cases were reported by Stevens[7] and Root. Metabolic rates varied from + 11 to a maximum of + 56 per cent above normal during height of diabetic coma. The calories calculated per hour varied from 60 to 100. During diabetic coma, energy needs are met from the oxidation of protein and fat. If 100 Gm. of glucose is given by vein, probably 75 to 90 Gm. of glucose is stored as glycogen or transformed into fat[8,9]; (4) to improve the synthesis of protein from amino acids.

If additional glucose is given during the first few hours of treatment, the substrate for insulin action is increased and the insulin requirement greatly increased. If sufficient insulin is given to overcome the resistance, then a correspondingly greater amount of glucose will disappear from the extracellular fluid and be deposited as glycogen or be transformed into fat. The deposit of glucose as glycogen is accompanied by a deposit of potassium and a corresponding withdrawal of potassium from the extracellular fluid. It is this hazard which is greatly increased by giving large amounts of glucose and the correspondingly greater amount of insulin which is required.[10] More important is the fact that if glucose is given in the first few hours, it becomes impossible to use the decline in blood sugar as a method of measuring insulin resistance. In the first six or eight hours of the treatment of diabetic coma, the most important single need is to ascertain the degree of insulin resistance and to overcome it by a sufficient dose of insulin. Recently, Seldin and Tarail,[11] in an important study of 12 cases of diabetic coma, showed that the giving of glucose in the early hours of coma, when the blood sugar level is already high, may increase the extracellular molarity and advance intracellular dehydration, with consequent renal failure. It must be remembered that with 1 Gm. of glycogen formed, 0.36 meq. potassium will be deposited.

When the blood sugar has fallen toward a normal level through the action of insulin, then glucose solutions may be employed with discretion.

Vitamins and antibiotics are frequently used. Antibiotics such as penicillin are used in unconscious patients in whom some hidden infection is suspected. Preparations of vitamin B complex may frequently be used during acidosis as a means of counteracting the tendency to, and the danger of, developing neu-

ropathy as a result of the severe acidosis. It must be admitted that no clear evidence of vitamin B deficiency is found in diabetic coma.

Complications of Diabetic Coma.—Hypoglycemia is often feared but seldom experienced in diabetic patients in whom every effort is made to begin the feeding of the patient within twelve or fifteen hours after admission. Our plan is to begin the oral administration of 10 Gm. of carbohydrate per hour within that period after admission. Under these circumstances hypoglycemia rarely is seen.

Circulatory collapse is evidence of the terminal stage. The blood pressure falls, the patient becomes pulseless, urinary secretion ceases, the respiration becomes shallow, and death may ensue.

Lipid Metabolism.—During diabetic coma or ketosis, severe disturbances of the lipid metabolism may be manifested by changes in the blood plasma. In some cases, the blood plasma may be creamy. The changes are characterized by a lipemia consisting principally of neutral fat, by hypercholesterolemia, and by varying degrees of lactescence. If the plasma is sufficiently rich in fat, the arteries and veins of the eyes may have a fatty appearance, such that the arteries and veins have the same color, a condition known as lipemia retinalis.

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Lipids of the blood are carried in the form of lipid-protein complexes. Gofman and his associates[12] have studied lipoproteins by an ultracentrifugal technique and found they could be separated into various classes or bands, designated as S_f 0-11, 12-20, and so forth, depending upon the density of the molecules. A series of 18 patients admitted to the New England Deaconess Hospital in diabetic acidosis or coma was studied by Tuller, Mann, Schertenleib, Roehrig, and Root.[13] Their results indicate very high values for the various lipoproteins during coma, with extraordinarily high values particularly for the S_f 100-400 components. In general, the high values for lipoproteins were paralleled by increases in cholesterol, although the changes in cholesterol were in some cases not nearly so marked as in the lipoproteins. Although dehydration and hemoconcentration played some part, it is evident that diabetic ketosis itself produces very extraordinary alterations in the serum lipids. The effects of treatment with insulin are very prompt; but not all patients return to normal levels within a short period of time. Although the degree of lipid disturbance associated with acidosis was varied, no patient failed to show some increase in the serum lipoprotein. This is particularly important in relation to the facts observed by Keiding, Mann, Root, Lowry, and Marble[14] whose study of young diabetic patients with diabetes of long duration showed that the high, abnormal levels of lipoproteins were associated with the most severe forms of diabetes and particularly lack of control of the diabetes. Early vascular disease and retinitis was most frequent in patients most severely out of control and with the higher lipoprotein values.

Lipemia retinalis was recently reported in a case of diabetic coma complicated by uremia by Kalinowski and Walker.[15] In the last twenty years, some 8 cases have been observed at the Deaconess Hospital,[16,17] and a total of something over 60 cases are described in the literature. In this condition, the retinal arteries and veins show, instead of the usual contrast in color, a similar creamy

color and often a silvery sheen. In a recent case, a boy, aged 17 years, with diabetes of nineteen months' duration, entered the Deaconess Hospital in early diabetic coma. The blood sugar value was 410 mg.; the plasma was creamy and the blood cholesterol value was 1,785 mg. He received 130 units of insulin in the first three hours and in the first twenty-four hours a total of 238 units. In the accompanying table are shown the serum lipoprotein values during a period of 45 days.

SERUM LIPOPROTEIN VALUES IN DIABETIC LIPEMIA

DAY	sf 12-20 (MG. PER CENT)	sf 21-35 (MG. PER CENT)	sf 35-100 (MG. PER CENT)
1	34	72	304
4	290	280	490
8	370	285	295
45	32	8	5

The Symptoms and Signs of Diabetic Coma.—The warnings of the onset of diabetic acidosis and coma are vague, and even to a doctor the diagnosis proves elusive. The diabetic patient who has not been following diet or receiving sufficient insulin may notice loss of weight, increasing thirst, and frequency in passing urine, and the urine tests may show a large amount of sugar present. Testing the urine for diacetic acid or acetone will give warning of the impending ketosis. Any unusual symptom such as headache, restlessness, weakness, nausea and vomiting, drowsiness, and, finally, the deep, painful, and rapid respiration of air hunger should arouse suspicion.

The patient shows striking chemical changes, including lowering of the carbon dioxide of the blood, marked elevation of the blood sugar, and the presence of positive tests for acetone both in the blood plasma and the urine. If he is unconscious, he will be restless or moaning, as if in pain, and will have dry, cold skin.

In the diabetic patient who has uremia as a cause for the low carbon dioxide of the blood, the eyeballs are not soft, vomiting may have been very prominent, blood sugar level may be high, but the elevated nonprotein nitrogen of the blood may be an important clue. The breath may be uriniferous instead of having the fruity odor of typical diabetic coma. The diagnosis of uremia in the diabetic patient is of great importance because such patients are not so resistant to insulin as true coma cases and an error in insulin dosage may be disastrous.

Prognosis.—Prognosis of diabetic coma depends first upon the age. Older patients with damaged kidneys and hearts have a more serious prognosis than children. Cases of long duration are more serious. The more severe the chemical changes or the longer the duration of unconsciousness, the more grave is the outlook. Severe neuropathies may follow coma, culminating in the triopathy of diabetes.[18]

Diabetic ketosis and coma produce an intracellular cyclone and the effects of acidosis and the lack of diabetic control may be manifest for long periods

thereafter. Thus, in some series, pulmonary tuberculosis has developed in 15 or 20 per cent of patients within five years after diabetic coma. In Table IV are shown the causes of death in 180 patients who have recovered from coma, left the hospital, and then were followed up. When comparison is made between the period from 1923 to 1946 and the last seven years, striking differences appear. Thus, nephropathy or chronic nephritis has become the cause of nearly 40 per cent of the deaths in the last seven years. These are patients with diabetes of long duration whose diabetic control has been poor. Coma itself recurred in some of the patients and caused death elsewhere. Pulmonary tuberculosis, formerly a common cause of death (nearly 25 per cent of the patients between 1923 and 1946) has fallen to less than 7 per cent in the later period.

TABLE IV. CAUSES OF DEATH IN 180 PATIENTS AFTER RECOVERY FROM COMA, 1923-1953

	1923–1946	1946–1953
Nephropathy	0	43
Coma	12	10
Cardiac (coronary sclerosis)	13	24
Tuberculosis	15	7
Miscellaneous	27	29
Total	67	113

The average duration of diabetes among the 180 patients was 14.1 years.

Prevention.—Every diabetic patient should be instructed how to test the urine for sugar and the necessity of daily tests. Control of diabetes by early use of insulin is basic. Finally, when a patient feels ill, he should be taught certain simple rules, as listed here.

1. Call a doctor.
2. Do not omit insulin unless the urine test is sugar-free.
3. Take a glass of warm liquid every hour.
4. Move the bowels.
5. Get a nurse.

The prevention of diabetic coma depends, finally, upon the discovery of diabetes in an early stage and its continuous control. At present, 12 to 15 per cent of all patients who have come to the New England Deaconess Hospital in diabetic coma did not know of their diabetes until acidosis developed. Actually, no child under 2 years of age has had the diagnosis of diabetes made until ketosis was present. The routine testing of the urine by all physicians in their offices, of all patients admitted to hospitals, and, finally, the Diabetes Detection Drive, sponsored by the American Diabetes Association, should result in the discovery of diabetes in an early and remediable stage before diabetic ketosis has occurred. The present practices of collecting the urine on the morning after admission to the hospital and doing blood sugar tests in the fasting state

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fail to disclose glycosuria and hyperglycemia which would be found if such routine blood and urine tests were required one to two hours after a full breakfast. The common causes of coma are preventable. The patients should be taught early that if insulin is missed, there is danger of coma. Irregularities of diet exceed by far any other cause of coma. It is the patient in poor control in whom mild infections lead rapidly to serious ketosis. Diabetic patients must not only be familiar with technical details of testing the urine, measuring the diet, and giving insulin, but they must understand the conditions under which ketosis may develop and should at all times be in communication with and under the care of a physician.

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ROENTGENOLOGIC FINDINGS IN SYSTEMIC LUPUS ERYTHEMATOSUS

An Analysis of 100 Cases

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SINCE there has been considerable interest at The Johns Hopkins Hospital in collagen vascular disease, we have had the opportunity to examine a large number of cases. Our colleagues have published results of their clinical experience to date.[1] We have thought it worth while to analyze and present 100 selected cases of systemic lupus erythematosus (S.L.E.)† from a roentgenologic standpoint.

The 100 cases were selected on the basis of certainty of diagnosis and completeness of radiologic coverage. Because of the cases rejected, this series is perhaps statistically weighted by more seriously ill patients, but the bias was somewhat counterbalanced by cases which were subtle diagnostic problems.

Those cases selected were proved by any or all of the following criteria: (1) necropsy, (2) biopsy, (3) L.E. cells, (4) typical clinical findings.

Table I. Distribution of Cases by Method of Proof

CRITERION FOR PROOF	NUMBER OF CASES
Necropsy	17
Biopsy	5
L. E. cells	56
Typical clinical findings	22
TOTAL	100

*Associate Professor.

**Assistant Resident.

†The series here reported omits some of the 138 cases studied by Harvey and his group, and includes a few others not contained in that series. The percentage incidence of observed radiologic abnormalities does not therefore exactly coincide with the data of the Harvey monograph.

ROENTGEN ANALYSIS

Pleura.—Pleural involvement was the most common finding in systemic lupus erythematosus. Seventy-four of the 100 cases had some type of pleural reaction during the course of their disease. Table II is an analysis of the type and location of the pleural reaction.

TABLE II. PLEURAL INVOLVEMENT IN 100 CASES OF S.L.E.

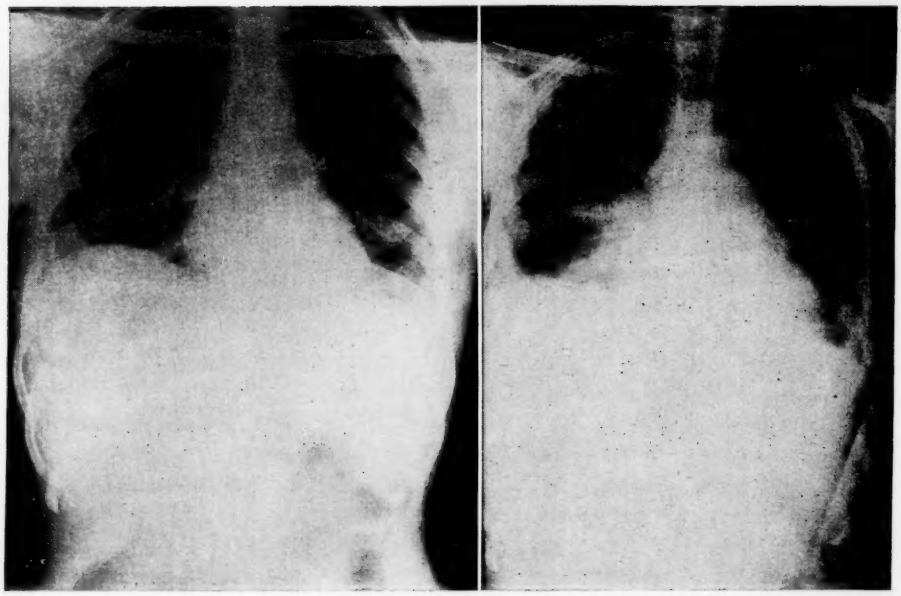
TYPE	RIGHT SIDE ONLY	LEFT SIDE ONLY	BILATERAL	TOTAL
Pleuritis	11	6	43	60
Small effusion	3	5	8	16
Massive effusion	1	1	0	2
Loculated effusion	3	0	0	3
TOTAL	18	12	51	81*

*Seven patients listed twice because of bilateral involvement with differing types of reactions: e.g., loculation, right; pleuritis, bilateral.

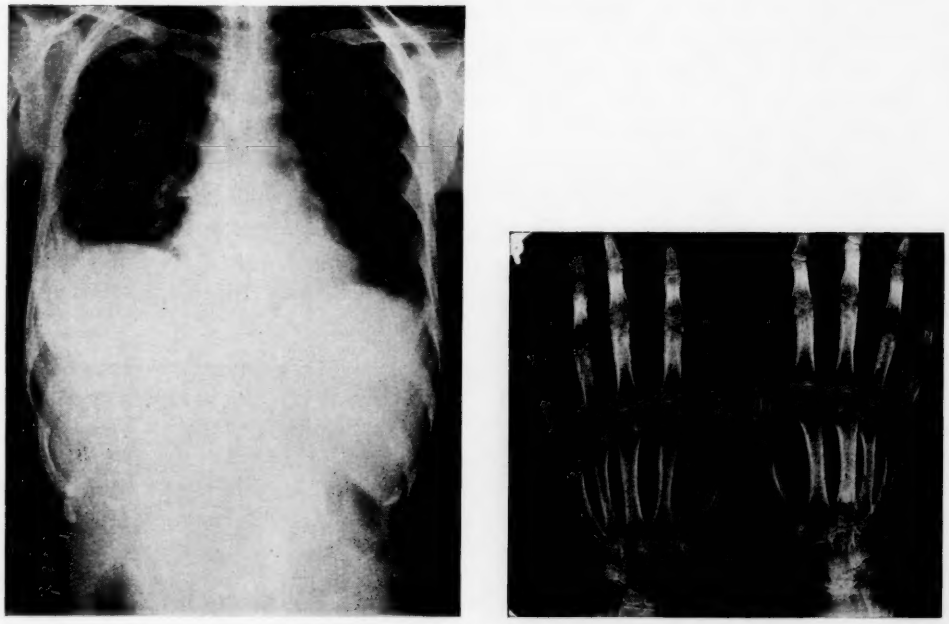
Pleuritis was recognizable on the chest roentgenogram as a shaggy thickening of the pleural surface (Figs. 1 and 2). The dependent pleural reflections and sulci tended to retain their angulation. The meniscus commonly associated with effusion frequently failed to appear even when considerable pleural reaction was present. We think that this quality of the pleuritis reflects the fibrinous nature of the reaction. This opinion is supported by the regularity with which fibrinous pleuritis appeared in the necropsy reports. In the majority of cases the pleural reaction was minimal. Rarely was it massive. If a massive pleural effusion is observed, it is wise to consider some superimposed infection even though the patient has proved systemic lupus erythematosus.

It is of particular interest that 51 per cent of our patients had bilateral pleural involvement. This finding is believed to be important in differential diagnosis since pleural reaction due to tuberculosis, infarct, and carcinoma is much more apt to be unilateral.

Lungs.—Just as the pleural involvement in systemic lupus erythematosus is unobtrusive, so is the lesion in the lung parenchyma.[2] Fifty patients had parenchymatous changes thought to be caused directly by S.L.E. The most common type observed was a focal patch of infiltration (Fig. 3, *A*). This lesion, when it occurred free of any pleural surface, was ill defined in both outline and substance. The patch was rarely dense or homogeneous, but instead was loosely reticular or granular and of low contrast. When the pneumonitis abutted the diaphragmatic pleura, elevation and sometimes tenting of the diaphragm occurred. Sixteen patients exhibited this phenomenon. A significant number of linear plaques were also encountered. These plaques formed horizontal bands, indistinguishable from compression atelectasis just above the diaphragm (Fig. 3, *B*), or radiated from the cardiophrenic sulcus in a manner radiologically identical to pulmonary infarction (Fig. 4). Two cases presented miliary in-



A. B.



C. D.

Fig. 1.—Case No. 439651. *A*, Chest roentgenogram (normal) shows splenic enlargement. *B*, Pleuritis and slight cardiac enlargement have appeared. *C*, Infiltration in the right upper lobe proved to be a staphylococcal abscess. *D*, Hands and wrists show only minimal changes despite severe clinical arthralgia.

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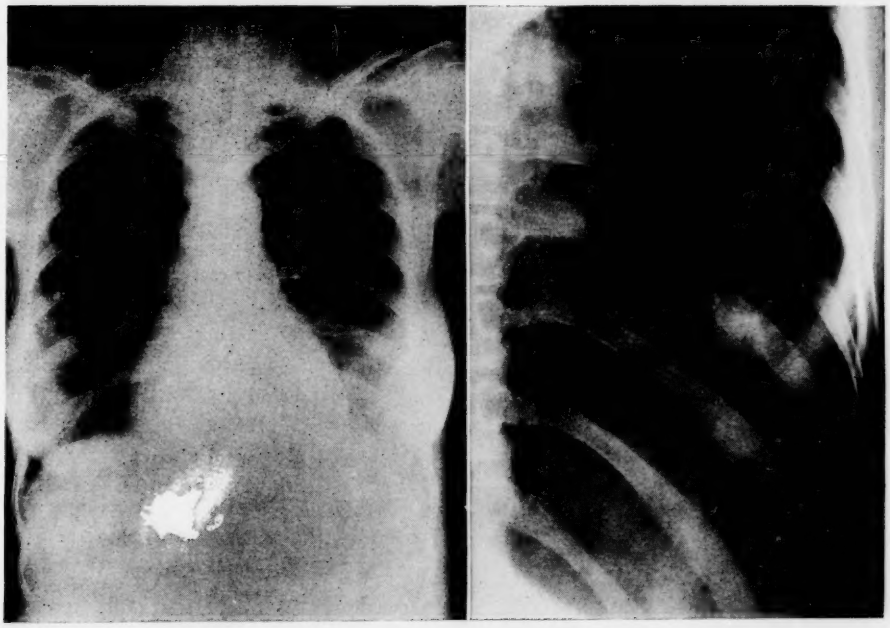
filtration; one of these was considered of S.L.E. origin because of negative bacteriologic studies and rapid clearance under cortisone therapy. The other case proved to have miliary tuberculosis at necropsy. One case presented the typical features of a purulent abscess but the material obtained by needle aspiration was sterile and contained large numbers of L.E. cells.

Both the focal patch of pneumonitis and the linear plaque have a slight tendency to involve both lungs. However, no marked predilection toward bilateral involvement, a noteworthy feature of pleuritis, has been found. It was significant that in 41 of 50 cases with pulmonary parenchyma changes, lesions were present in the lower lobes.



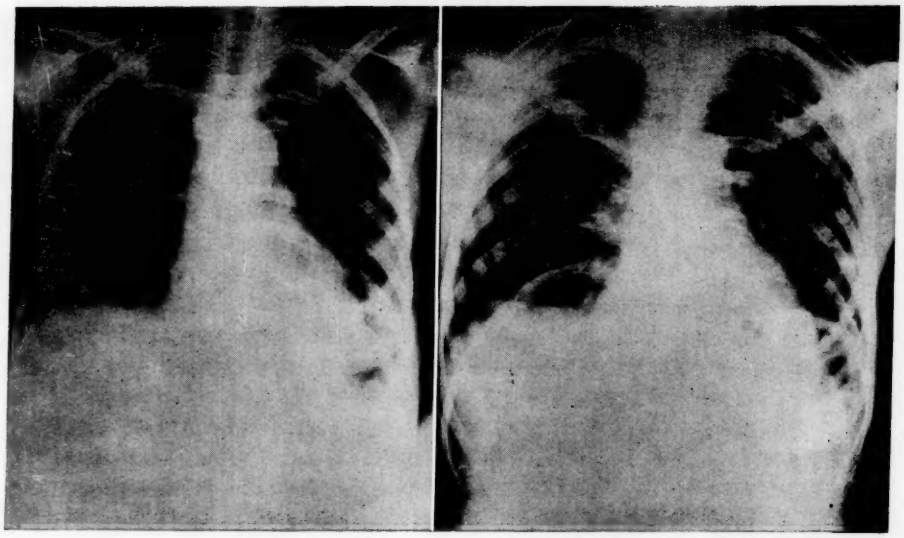
A. *B.*

Fig. 2.—Case No. 641028. *A*, Slight cardiac enlargement and bilateral pleuritis. *B*, Coned-down view illustrates the fibrinous character of the pleuritis.

TABLE III. LUNG PARENCHYMA INVOLVEMENT IN 100 CASES OF S.L.E.

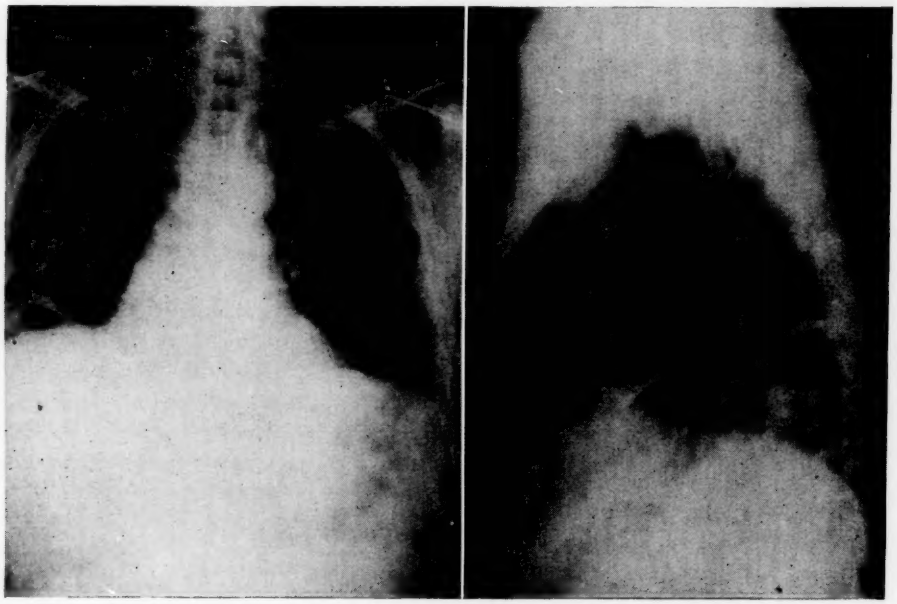
TYPE	RIGHT SIDE ONLY	LEFT SIDE ONLY	BILATERAL	TOTAL
Focal patch	15	9	15	39
Linear plaque	5	2	4	11
Miliary	0	0	1	1
"Abscess"	1	0	0	1
TOTAL	21	11	20	52*

*Two patients listed twice because of bilateral involvement with differing types of reactions: i.e., focal patch, right; linear plaque, left.



A. *B.*

Fig. 3.—Case No. 655032. *A*, An ill-defined patch of pneumonitis at the right base and minimal bilateral pleuritis. *B*, Same case one year later shows a plaque of pneumonitis at the right cardiophrenic angle and patches of infiltration in the left lower lung field.



A. *B.*

Fig. 4.—Case No. 501114. *A*, Posteroanterior and, *B*, lateral chest roentgenograms showing bilateral bands of pneumonitis indistinguishable from pulmonary infarctions.

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Heart.—Cardiac involvement was present in 53 per cent of the patients studied. Three cases had gross pericarditis revealed as a hydropneumopericardium after pericardicentesis. The 50 patients who showed cardiac enlargement with rapid and sometimes pronounced variation in size or configuration (Figs. 1 and 5) were classified "carditis." The reasons for the use of this term will be dwelt upon in the discussion.

Roentgen phenomena related to cardiac decompensation were observed in 33 patients. Eleven cases of pulmonary congestion and eight cases of dilatation of the azygos vein were noted. The former presumably indicated left, and the latter right, ventricular decompensation. There were 14 examples of edema of the soft tissues manifested by subcutaneous swelling and blurring of the cleavage planes. It was not determined which factor or combination of factors was responsible: right heart failure, nephritis, or cortisone therapy. In 6 patients (all of whom were in fact hypertensive) cardiac enlargement of typical hypertensive configuration was present. These cases probably represent coincidence of benign hypertension, but a causal relationship with S.L.E. nephritis cannot be excluded.

Joints.—That arthralgia is a prominent symptom in systemic lupus erythematosus is attested by the fact that 64 joint examinations on 43 patients were obtained in our series. In 26 patients some aberration from the normal was found on the roentgenograms. Changes most frequently observed were soft tissue atrophy and osteoporosis of minimal degree. In only one case was there narrowing of the joint space, subluxation and ulnar deviation of the fingers, typical of rheumatoid arthritis. Except for this last case it must be emphasized that almost all the changes observed were minimal in degree and frequently had not been commented upon in the initial interpretation. Studies of the axial skeleton such as skull, spine, and pelvis were of no diagnostic aid.

Abdomen.—Other than a slight degree of splenic enlargement which was encountered in 34 per cent of the patients, the examination of the abdomen was unproductive. Even splenic enlargement was more often detected on a well-exposed chest film than on the abdominal roentgenogram.

Six patients had evidence of fluid in the abdomen. Not one had massive ascites. Two patients had evidence of ileus or distention. Gastrointestinal symptoms impressed the clinician so that 29 upper gastrointestinal studies,* 16 gall-bladder series, and 10 barium enemas were obtained. These examinations were largely normal and no findings pertinent to systemic lupus erythematous were uncovered, nor were any esophageal lesions suggestive of scleroderma observed. Intravenous pyelograms were obtained in 16 patients and 4 showed evidence of diminished renal function. This functional impairment is the only roentgen finding which may conceivably be directly related to the characteristic glomerular necrosis ("wire loop") of systemic lupus erythematosus. It cannot be considered of real diagnostic significance.

*Some of these were requested because of possible complications of steroid hormone therapy.

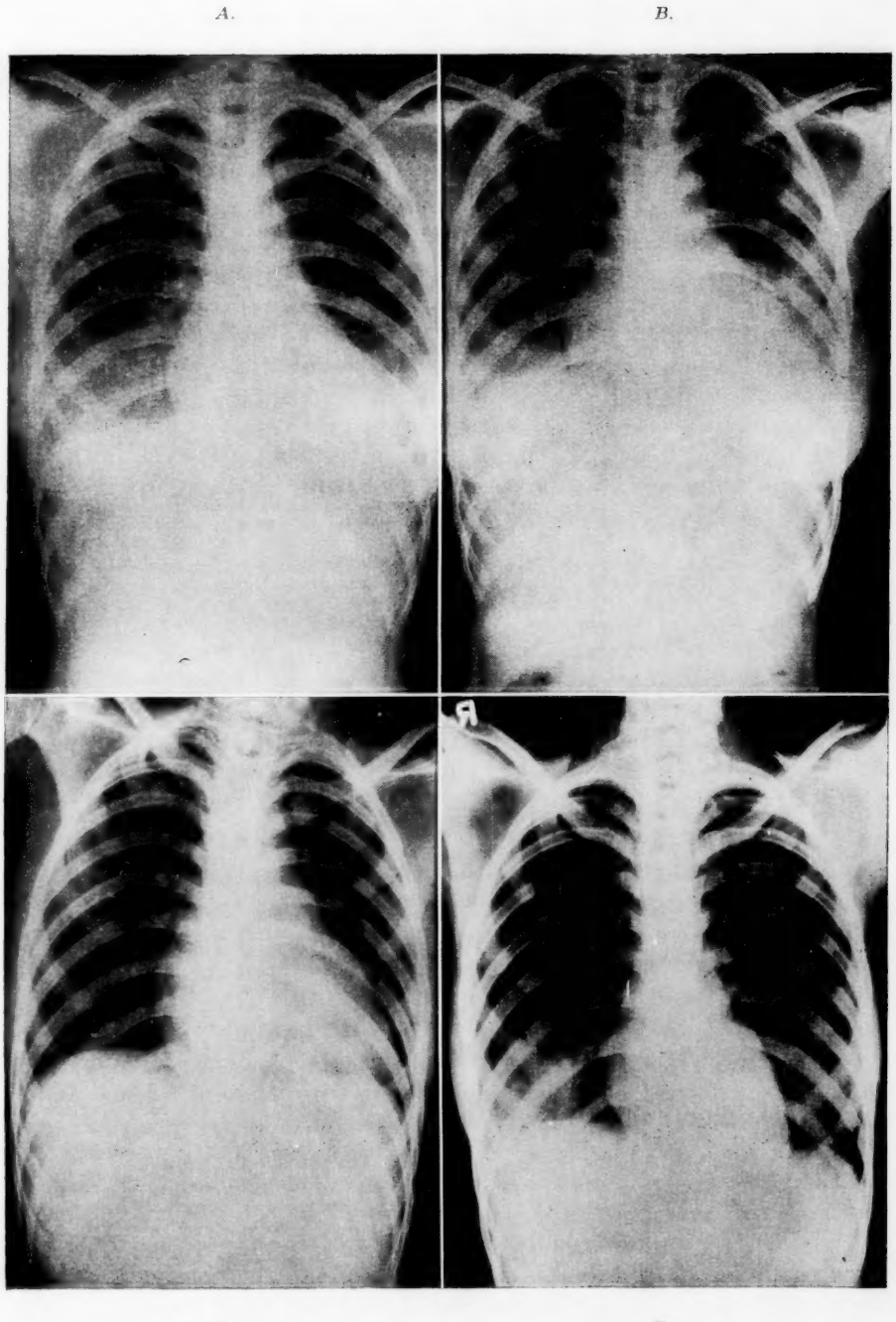

Fig. 5.—Case No. 532508. *A*, *B*, *C*, and *D*, Serial chest roentgenograms illustrating fluctation in cardiac size and configuration. *B*, Bilateral pleuritis is also present. *D*, Pneumonitis has appeared at the right base.

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Sinuses.—Of more than passing interest was the frequency of sinusitis. Sixteen patients had roentgen examinations of the paranasal sinuses. Mucous membrane thickening, fluid levels or polyp formation were observed in 7 cases.

Secondary Infections.—Since S.L.E. markedly reduces the patient's normal resistance to disease, one must be constantly on the alert for roentgenologic evidence of secondary infection. In our series, two patients had overwhelming tuberculosis (1 miliary and 1 massive pleural effusion); and 5 patients had serious superimposed staphylococcal infections (2 pulmonary abscesses, 2 pneumonitides, and 1 bacterial endocarditis). Failure to recognize these conditions and consequent continuation of hormone therapy may have contributed to the fatal outcome in 3 cases.

Incidental Disease.—One case each of the following diseases was found in our series: silicosis, large calcified tuberculous nodes, esophageal varices, duodenal ulcer, cholelithiasis, tubo-ovarian abscess, rheumatic heart disease, and syphilitic heart disease.

DISCUSSION

Although there is no one specific radiologic feature which is distinctive, nonetheless the presence of systemic lupus erythematosus may be strongly suspected on the basis of roentgen studies. A well-defined constellation emerges particularly when a chronologic sequence of chest roentgenograms is available. While each individual part of this constellation is not in itself characteristic of the disease, the aggregate becomes almost diagnostic of systemic lupus erythematosus.

The most constant feature of S.L.E. is pleuritis, which is usually minimal, bilateral, and fibrinous.

Pneumonitis is the most perplexing element of the constellation. To the radiologist, it is at times a small patch, ill-defined and difficult to describe; at other times, there are linear bands or plaques resembling pulmonary infarction or compression atelectasis. To the clinician, a lingering pneumonitis with low-grade fever and no apparent response to antibiotics so frequently suggests "virus pneumonia" that this error is virtually a characteristic feature of the patient's history. Even the pathologist is led astray by the nuances of lupus pneumonitis. In only one of the 17 autopsied cases was pneumonitis attributed specifically to systemic lupus erythematosus. Such interpretations as antibiotic-aborted pneumonia, anaphylactoid pneumonia, and virus pneumonitis occurred regularly in the protocols.

Cardiac involvement is the third member of the constellation. In our series a number of cases demonstrated startling variation in the size and configuration of the heart. Occasionally pronounced variations occurred within a period of days. The relationship of such variations to steroid hormone therapy could not be determined. We consider this phenomenon the most significant roentgen evidence of "carditis" due to systemic lupus erythematosus.

Both the clinican and the roentgenologist, when confronted with sudden cardiac enlargement, tried to sift the evidence which favored pericarditis or myocarditis, and usually no satisfactory conclusion could be reached.

With this in mind, the autopsy data were analyzed. Most cases that died with systematic lupus erythematosus had, from a pathologist's viewpoint, a pancarditis. Thirteen examples of cardiac enlargement (7 slight, 6 marked) were found among 17 necropsies. The endocarditis was of the Libman-Sacks' type, a minimal lesion which rarely causes functional impairment let alone gross cardiac enlargement. The pericarditis, in common with other serous inflammatory changes, presented as a scanty fibrinous exudate. At times, there was slight thickening of the pericardium with delicate adhesions present. Occasionally small amounts of fluid were found, but in our material only rarely were massive effusions encountered unless a secondary infection supervened (2 cases of purulent pericarditis). It was concluded, therefore, that the accumulation of pericardial fluid is not an important factor in the sudden increase in heart size in uncomplicated systemic lupus erythematosus.

If, then, endocarditis and pericarditis are excluded, one is forced to turn to myocarditis as an explanation of the fluctuating heart size. Myocarditis is detected by the pathologist as microscopic areas of fibrinoid degeneration and collections of perivascular round cells. It would have been a comfort to us if the pathologist had found, in these cases, severe myocarditis accompanied by a mild pericarditis and endocarditis. It was disconcerting, however, to find that histologically the myocarditis paralleled the endocarditis and pericarditis in the paucity of changes. Nonetheless, with the exclusion of pericarditis and endocarditis as common causes of variability in heart size, there is no recourse but to implicate the myocardium in some way. Perhaps systemic lupus erythematous produces a physiologic impairment and elongation of the muscle fibers rather than gross morphologic and histologic changes. Therefore, in order to symbolize cardiac involvement due to a pancarditis in which the pericarditis and endocarditis play a minor role, the term "carditis" was adopted.

Incongruity is the outstanding feature of the fourth member of the constellation, i.e., joint changes. While the roentgenograms may be interpreted as either normal or showing a minimal degree of osteoporosis and soft tissue atrophy, the patient may have an impressive history of disabling, painful, hot and swollen joints. Clinically the exact pattern of rheumatoid arthritis may be duplicated, but the roentgenographic pattern mimics only the early stages of rheumatoid disease. We believe that the joint changes of S.L.E. are reversible, that destruction of cartilage or bone does not occur. A fibrinous synovial effusion similar to the effusions encountered in the pleural and pericardial spaces might well be responsible for the arthritis of systemic lupus erythematous.

The observation of a slightly enlarged spleen renders the constellation complete. It should be stressed that roentgenographic evidence of any combination of pleuritis, carditis, pneumonitis, and splenomegaly was frequently present through unsuspected by the clinician.

This pattern of roentgenographic events is not felt to be an artificial constellation but rather to reflect an underlying pathologic process. The pleura, pericardium, peritoneum, and probably the synovia are involved in a special kind of serositis which can and frequently does resolve without scar tissue formation or any irreversible damage. Instead of the production of large effusions

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a meager substance is exuded. This material is high in protein and its fibrinous nature suggests preferential exudation of fibrinogen through the vascular bed and serous membranes. Blood from patients with S.L.E. occasionally has unusual clotting and sedimentation characteristics and frequently gives false positive serologic tests for syphilis.[3] In addition the serum is capable of changing polymorphonuclear leukocytes from normal individuals into L.E. cells. It is not unusual to encounter these changes in the blood even before the patient becomes ill. It may be concluded that an abnormality in the metabolism of proteins, particularly globulin and fibrinogen, is one of the earliest manifestations of systemic lupus erythematous. Is it possible that collagen vascular lesions in S.L.E. are the morphologic manifestations of a more fundamental process which alters protein metabolism?

SUMMARY

A five-membered radiographic constellation is characteristic of S.L.E.: (1) minimal bilateral fibrinous pleuritis; (2) ill-defined patches or linear bands or plaques in the lung bases; (3) fluctuation in the size and configuration of the heart; (4) slight enlargement of the spleen; (5) conspicuous lack of irreversible structural damage to the joints.

The first four can be seen frequently on serial chest roentgenograms. Table IV is a statistical summary of these findings.

TABLE IV. ROENTGEN MANIFESTATIONS OF S.L.E. IN 100 CASES

ORGAN OR TISSUE INVOLVED	USUAL MANIFESTATION	PER CENT OF PATIENTS FOUND POSITIVE
Pleura	Pleuritis	74
Lung	Pneumonitis	50
Heart	Carditis	53
Spleen	Slight enlargement	34
Joint	Minimal osteoporosis	26

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THE CLINICAL SIGNIFICANCE OF END-TIDAL NITROGEN CONCENTRATION DURING OXYGEN BREATHING

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AFTER breathing pure oxygen for a few minutes, the 81 per cent nitrogen normally present in the lungs is almost completely replaced. There will, however, remain a small residue of nitrogen derived from body tissues via the blood stream. This transfer of nitrogen from body tissues to lung air will continue until the tissue nitrogen pressure equals the partial pressure of the lung nitrogen, or for about 6 hours.[1]

Cournand and his associates[2] have shown that after breathing pure oxygen for 7 minutes the lung nitrogen normally reaches a minimal concentration not exceeding 2.5 per cent. These investigators found that when the intrapulmonary mixing of inspired gas is faulty, the alveolar nitrogen concentration at the end of 7 minutes of oxygen breathing is above 2.5 per cent; hence they termed this 7-minute alveolar nitrogen concentration an "index of intrapulmonary mixing." The variables determining this index appear to be the residual and dead space volumes, the rate and depth of breathing, and the evenness of alveolar ventilation. While marked impairment of intrapulmonary mixing raises the alveolar nitrogen concentration determined after 7 minutes of pure oxygen breathing, lesser degrees of impairment may not be reflected in an abnormality at this point. Some observers have preferred to collect the sample at an earlier time. Fowler[3,4] and Comroe[5] have recently reviewed the theoretical implications of the method.

With the development of commercially available recording nitrogen meters, exploration of the breath-by-breath decrease in end-tidal expired nitrogen concentration during pure oxygen breathing became possible. By simultaneously recording the air flow pattern using a pneumotachograph (Fig. 1), a detailed analysis of the intrapulmonary distribution of inspired gases can be made. Experimental and theoretical studies of these nitrogen concentration curves have been carefully developed in several laboratories,[3,6,7] but the simple accumulation of clinical data is needed to answer several questions. What can be learned

*Some of the observations reported here were made by one of the authors (G.E.D.) in partial fulfillment of the requirements for the degree of Doctor of Medicine.

concerning the diagnosis and course of pulmonary disease by using this technique? Is the entire 7-minute curve necessary to provide information of clinical value, or will one or two spot samples obtained in the course of 7 minutes of oxygen breathing suffice? If one or two samples are adequate, when should they be obtained to be of greatest value?

As a contribution to the eventual answering of these questions the present report deals with an analysis of a group of pulmonary nitrogen concentration curves* and their relation to clinical factors and other pulmonary function tests.

MATERIAL

The data included in this report represent 134 studies on 65 patients with a variety of chronic pulmonary diseases who had been referred to the Cardiopulmonary Laboratory. The diseases include pulmonary fibrosis, emphysema, bronchial asthma, pneumoconiosis, and sarcoidosis. An additional 18 studies on 12 normal volunteers from the professional and technical population of the hospital are included. Finally, 6 patients were studied before, and one and two months after, the surgical removal of one or more lobes of the lung.

METHODS

Maximal breathing capacity and lung volumes (except functional residual capacity) were determined by using a recording 9 liter bell spirometer. The functional residual capacity was estimated by a modification of the technique of Darling, Courtnand, and Richards.[6] At the same time that the functional residual capacity was being determined, a continuous nitrogen analysis of expired air was recorded by means of a Hervy-Lilly type nitrogen meter (sensitive to ± 0.2 per cent nitrogen down to 0 per cent), and, in some cases, a simultaneous pneumotachogram was recorded (Fig. 1). End-tidal nitrogen concentration was used for plotting the pulmonary nitrogen concentration curve, recognizing that it might not reflect true alveolar nitrogen. However, the difficulty of getting patients with advanced emphysema to perform deep expiration in a uniform manner made the more uniform end-tidal level seem preferable.

Arterial blood oxygen saturation was estimated by means of an earpiece oximeter during ambient and pure oxygen breathing. In some cases the tests were repeated after Vaponefrin inhalation, or inspiratory intermittent positive pressure breathing, and in 6 cases, one and two months after pneumonectomy or lobectomy.

Because the number of studies was large, a table containing all of the individual observations would be unmanageable. Therefore much of the data has been expressed in terms of correlations or mean values with calculated standard deviations.

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*Hereafter in this report the phrase "pulmonary nitrogen concentration curves" will refer to end-tidal nitrogen concentrations plotted against a 7-minute time period of oxygen breathing.

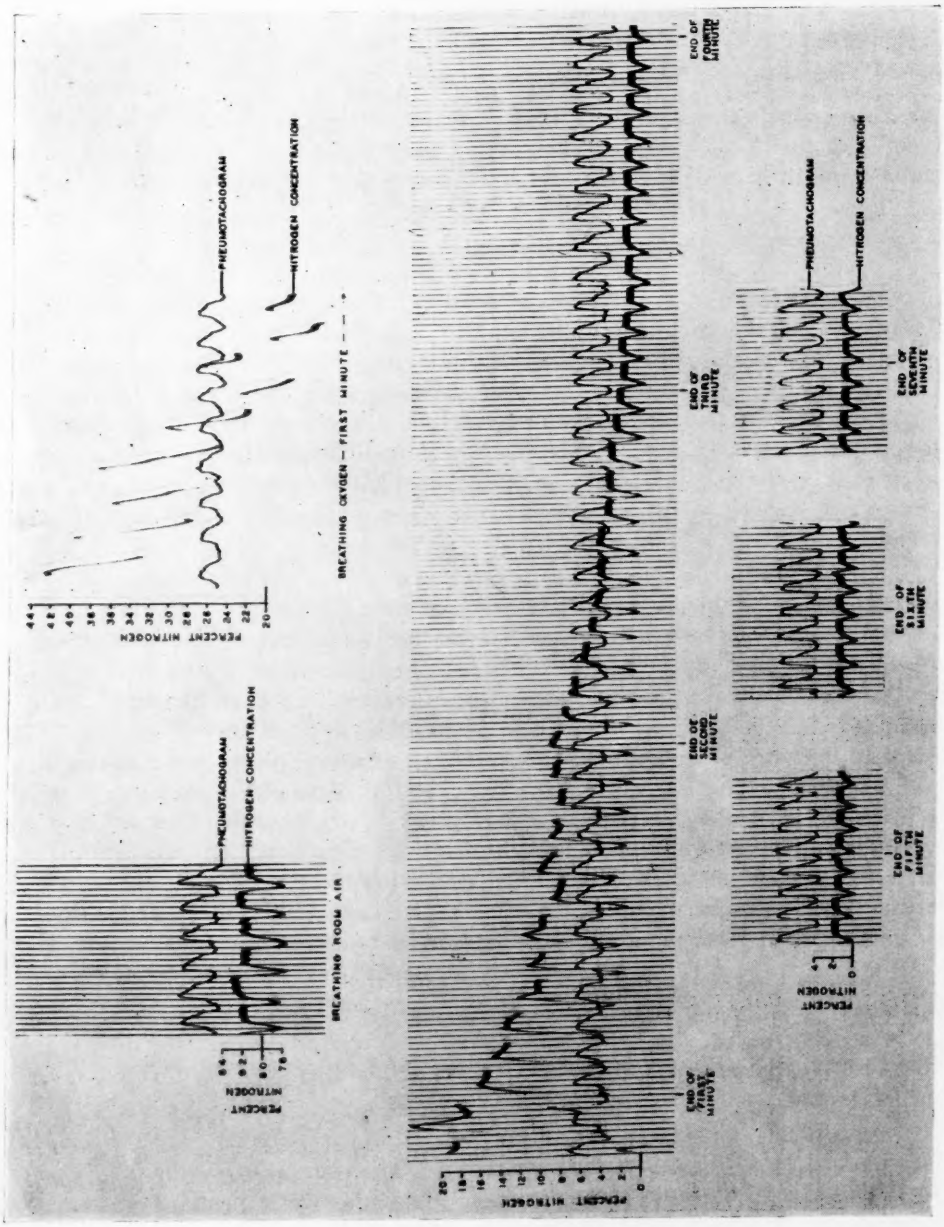

Fig. 1.—A continuous expired nitrogen concentration curve plotted during 7 minutes of oxygen breathing. A simultaneous pneumotachogram showing tidal velocity is plotted on the same graph.

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RESULTS

The normal subjects were deliberately chosen from a young age group; thus "normal" implies "healthy" rather than average or mode. Further to exclude clinically unrecognized lung disease, only subjects whose standard pulmonary function tests were entirely within a normal range were accepted.

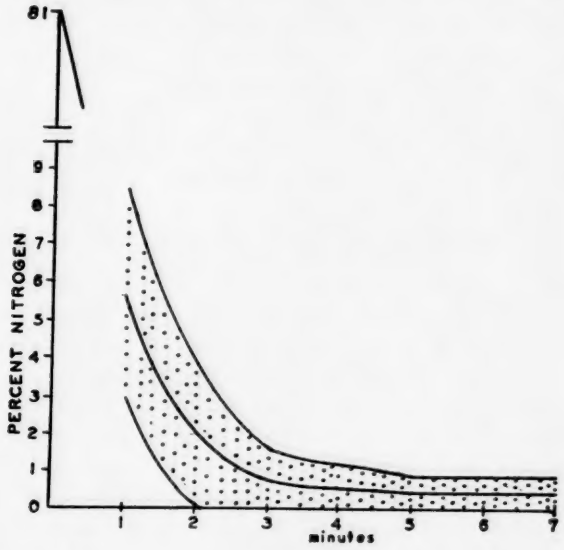

Fig. 2. Mean end-tidal nitrogen concentration curve of normal subjects during oxygen breathing. The stippled area represents twice the standard deviation on either side of the mean.

Fig. 2 shows the pulmonary nitrogen concentration curves representing the mean of the normal group and twice the standard deviation on either side of the mean. During the first 2 minutes the spread is great. This variability probably reflects variation in the individual rate and depth of respiration during the initial phase of oxygen breathing. At the third minute the mean end-tidal nitrogen concentration is below 0.91 per cent, with a probable range of 0 to twice the standard deviation, or 0 to 1.57 per cent; at the fourth minute a range of 0 to 1.17 per cent; and, from the fifth minute on, stable at 0 to 0.87 per cent.

In none of the 65 patients studied were normal values found for all of the routine pulmonary function tests, although in some cases only one or two out of the battery of tests were abnormal. On inspecting the table of ranges for end-tidal nitrogen concentration (Table I) it is apparent that none of the patients reached a nitrogen concentration of 0 per cent before the fourth minute, but from then on increasing numbers reached this level, hence the fourth minute was chosen for more intensive analysis.

When the end-tidal nitrogen concentration at the end of the fourth minute is considered, it is found to correlate very well with both the residual volume and the functional residual capacity, the correlation coefficient, r, of both being +0.75 with a standard error of r of 0.15. On the other hand, there is no signifi-

TABLE I. RANGE OF END-TIDAL NITROGEN CONCENTRATIONS OBSERVED IN 134 STUDIES ON 65 PATIENTS

	MINUTE						
	1	2	3	4	5	6	7
Maximum N_2 Conc., %	35	18	13.4	10.4	10.4	8.4	7.0
Minimum N_2 Conc., %	3	1.6	0.6	0	0	0	0

cant correlation with the resting arterial oxygen saturation, the maximal breathing capacity, the expiratory reserve volume, or the ratios of the functional residual capacity and the residual volume to the total lung capacity. The correlation with the resting arterial oxygen saturation approaches 0, with an r of 0.018.

Having only 65 unselected patients with chronic pulmonary disease it is difficult to divide the group into types of disease and still to have significant numbers of patients representing each type. However, it was possible to isolate a group of 11 young patients with pulmonary sarcoidosis* and compare this group with another group of 11 patients in the same age range who had relatively pure emphysema. These patients were all 20 to 30 years of age, as were the 12 normal subjects. When the mean pulmonary nitrogen concentration curves of the 3 groups are plotted together (Fig. 3), a considerable difference is found, and at the fifth minute, a range twice the standard deviation on either side of the mean overlaps only slightly from one group to another.

Pulmonary nitrogen concentration curves were determined for 22 patients before and after Vaponefrin inhalation. Of these, 13 had improvement in most of their pulmonary functions, with an average decrease in the functional residual capacity of 0.850 liter. The average level of their end-tidal nitrogen concentration at the fourth minute was 0.97 per cent less than before Vaponefrin; 1.15 per cent less at the fifth minute; and 0.77 per cent less at the seventh minute (Fig. 4).

For 23 patients, pulmonary nitrogen concentration curves were determined before and after the use of inspiratory intermittent positive pressure breathing (hereafter called Insp.P.P.B., the word "intermittent" being omitted since "inspiratory" implies "intermittent"). In 12 cases (Fig. 5) a significant rise was observed in the functional residual capacity after 20 minutes of Insp.P.P.B., suggesting that an impairment of the total resilient qualities of the lung would not permit it to return promptly to the resting volume after overdistention by Insp.P.P.B. The average increase in the functional residual capacity was 0.873 L., while the average fourth minute end-tidal nitrogen concentration increased 0.77 per cent; the fifth minute end-tidal nitrogen concentration increased 0.35 per cent; and, at the seventh minute, it had increased 0.22 per cent. Eleven of

*Other cases of sarcoidosis were in the series, but because these patients were of an older age, emphysema as a concomitant became likely.

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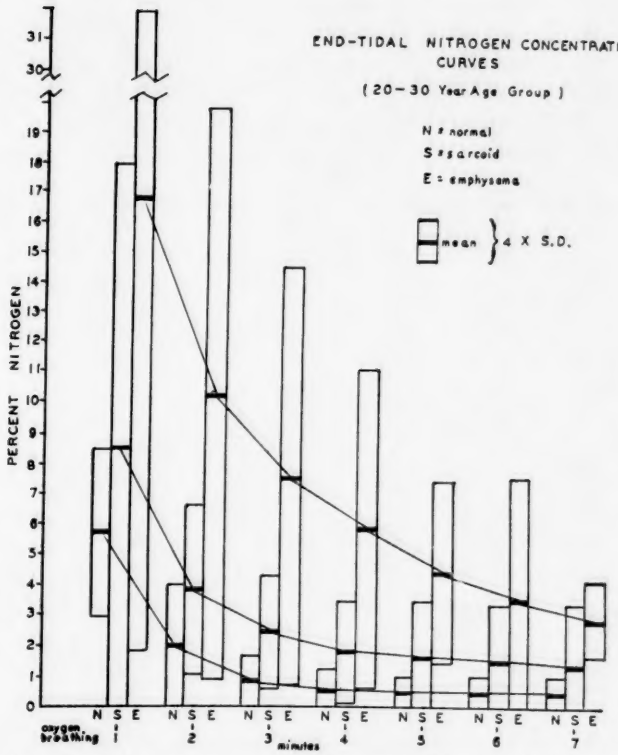

Fig. 3.—End-tidal nitrogen concentration curves of normal subjects, patients with sarcoidosis, and patients with emphysema, all in the 20- to 30-year age group.

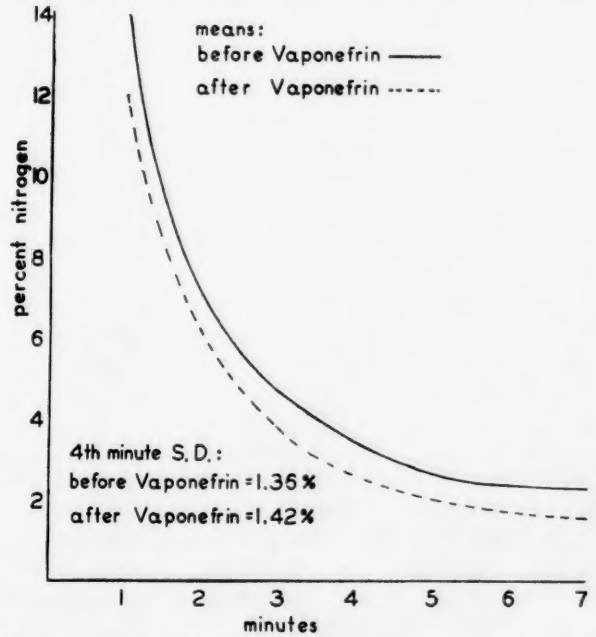

Fig. 4.—The effect of Vaponefrin inhalation on end-tidal nitrogen concentration curves. Thirteen cases in which function improved after Vaponefrin.

the patients (Fig. 5) treated with Insp.P.P.B. showed an immediate drop in the functional residual capacity averaging 0.771 L. In this group the fourth minute end-tidal nitrogen concentration dropped an average of 0.2 per cent, whereas the fifth minute average revealed no change and the seventh minute average was increased 0.2 per cent.

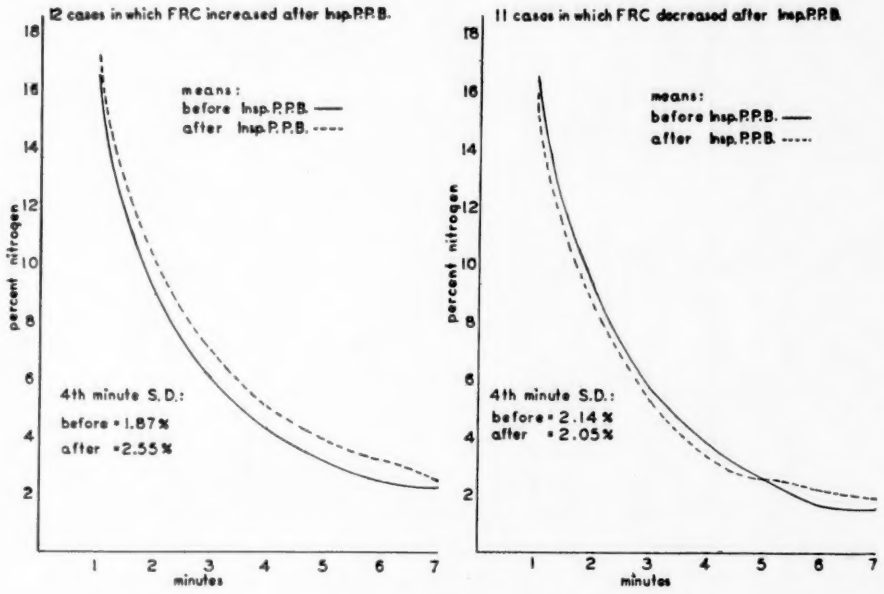

Fig. 5.—The effect of inspiratory positive pressure breathing on end-tidal nitrogen concentration curves.

In most of the surgically treated cases (except Case A) the total lung capacity dropped, as might be expected. The decrease occurred in some cases in the inspiratory capacity, and in these the ratio of the residual volume to the total lung capacity increased at least temporarily. Fig. 6 demonstrates that the end-tidal nitrogen concentration at the fourth, fifth, and seventh minutes sometimes, but not always, reflected the change in the ratio of the residual volume to the total lung capacity. In the one case (Case B) in which the end-tidal nitrogen concentration did not follow the ratio of the residual volume to the total lung capacity, a considerable absolute decrease in the residual volume was found. This may have influenced the end-tidal nitrogen concentration, although a pneumotachogram was not done on this patient, hence a change in tidal breathing pattern cannot be excluded.

DISCUSSION

A test of pulmonary function may serve either as a clinical indicator of the type or severity of pulmonary disease, or as a research technique to illuminate the physiologic processes involved in lung disease. The decreasing concentration of expired nitrogen during oxygen breathing may be used as a research tool if it is carefully plotted against a single tidal volume[8] or a sequence of breaths.[9]

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These methods are, however, somewhat too cumbersome for routine clinical use, and the purpose of the present study is to estimate the possible clinical value of one or two isolated end-expiratory nitrogen determinations obtained during a seven-minute oxygen breathing period as an indicator of an important aspect of pulmonary function.

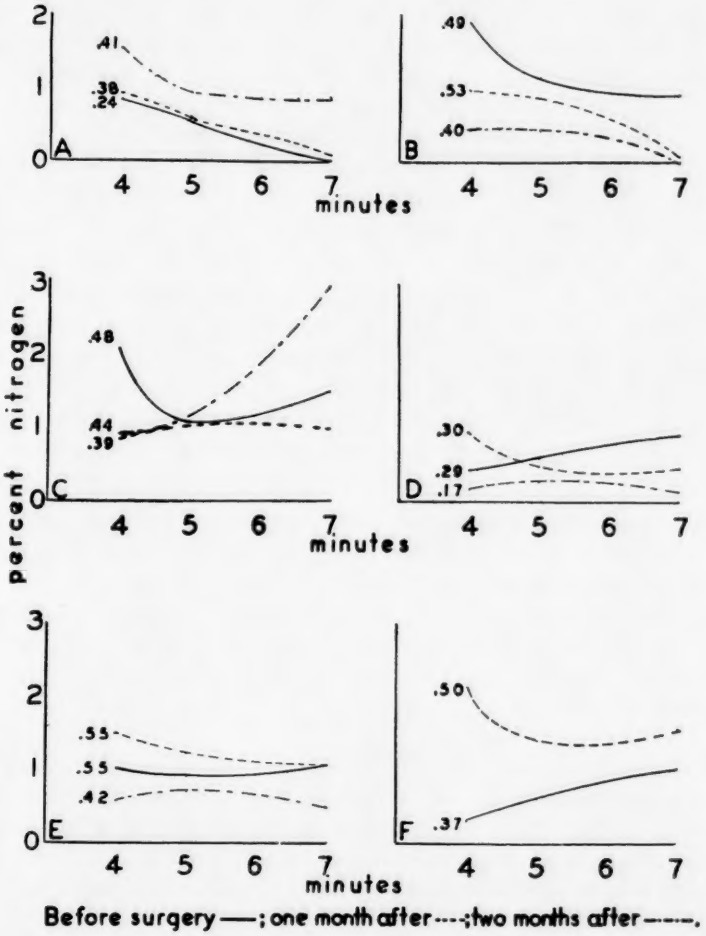

Fig. 6.—End-tidal nitrogen concentration curves before and after thoracic surgery. The decimal fractions on the curves indicate the ratio of residual volume to total lung capacity. The rise in nitrogen concentration seen in some of the curves is exaggerated by the scale employed. Small rises such as are seen here are probably due to an increase in tidal ventilation that often develops after a few minutes of breathing pure oxygen.

During the first few minutes of oxygen breathing considerable variability has been found in the rate and depth of respiration, producing erratic values for alveolar nitrogen concentration. This is reflected in the large standard deviation for both normal and pathologic cases (Fig. 2). On the other hand, toward the seventh minute, all curves tend to reach a low level. Hence in an initial effort

to evaluate a patient's pulmonary function, points in the middle of the curve should prove most fruitful. Theoretical reasons could be advanced for choosing the fourth minute, since Boothby, Lundin, and Helmholtz found the nitrogen washout time in a closed circuit to be 2 to 3.5 minutes[7]; and in our experience the values obtained at this period correlate very well with the degree of pulmonary distention or emphysema. In the younger age group (Fig. 3) the fifth minute appears to offer better separation of the ranges for emphysema, sarcoid, and normal. This seems to be due to the circumstance that the data are more closely grouped around the mean in the young emphysema group. Since the means themselves are actually closer together at the fifth minute, it would not be valid to say that an isolated sample at the fifth minute would offer better differentiation of these groups than one at the fourth minute. On the other hand, the improvement in nitrogen elimination after breathing Vaponefrin was slightly more obvious at the fifth minute than at either the fourth or the seventh minute.

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The decrement of alveolar nitrogen concentration observed after a subject begins to breathe pure oxygen depends upon intrapulmonary gas mixing, but the dynamic variables are tidal volume and respiratory rate. Time, in minutes, merely serves, in a rough way, to estimate a composite value for these two variables. Since measuring nitrogen removal as a function of tidal volume (as, for instance, during a single breath of oxygen) requires elaborate apparatus, it will not often be done in the routine evaluation of pulmonary insufficiency.

The analysis of a single alveolar sample at the end of expiration is, in contrast, a relatively simple procedure. Although not, in itself, distinctly better than other tests of pulmonary function, it will often confirm otherwise uncertain data, and may prove an especially sensitive means of following the progress of therapy. An alveolar sample obtained at the end of 4 or 5 minutes of pure oxygen breathing would appear to provide maximum information if only a single analysis is to be made.

SUMMARY

1. The technique of plotting end-expiratory nitrogen concentration during 7 minutes of oxygen breathing against a time coordinate as a measure of pulmonary function was applied in 134 studies on 65 patients.

2. The results correlated well with residual volume and functional residual capacity estimations, but not with arterial blood oxygen saturation.

3. A single end-expiratory sample obtained between the fourth and fifth minutes of oxygen breathing provides virtually the same information as a series of many samples obtained at intervals during the entire 7 minutes.

4. The single sample technique provides a sensitive indicator of change in pulmonary function due to bronchodilators, surgical resection of part of the lung, and inspiratory positive pressure breathing. In regard to the latter, it is of interest to note that pulmonary nitrogen elimination is frequently impaired after Insp.P.P.B. because the lung does not return readily to its resting volume.

The authors wish to acknowledge the technical assistance of Mrs. Dolores Mould and Miss Dian Teveliet.

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THE ISOLATION OF UNIDENTIFIED PLEOMORPHIC BACTERIA FROM THE BLOOD OF PATIENTS WITH CHRONIC ILLNESS

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THE interpretation of the significance of bacteria isolated from the blood of patients with chronic illness remains a problem for the clinician. In an attempt to determine the relationship of such organisms to the clinical syndromes with which they are associated, special studies were undertaken, not only to improve the effectiveness of blood culture techniques, but further to evaluate the presence of bacteria in the circulating blood of patients with chronic illness. Although many of the species of bacteria recovered from such patients can be readily identified by standard laboratory procedures, definite identification of others is most difficult.

This report is concerned primarily with an organism of the latter type which has been recovered from a number of patients with chronic illness, and has been designated unidentified pleomorphic bacterium (UPB).

MATERIALS AND METHODS

The UPB were isolated in the following manner. Blood was obtained from 100 patients with chronic illness and, for control, from 50 persons considered to be normal. A total of 20 ml. of blood was obtained by venipuncture after careful disinfection of the skin with alcohol and iodine. Five milliliters of blood were distributed to each of the following:

1. A flask containing 75 ml. of tryptose-phosphate broth (Difco).
2. A flask containing 75 ml. of trypticase-soy broth (BBL).
3. A two-ounce bottle containing a slant of enriched Albimi's brucella agar[1] the base of which was immersed in 10 ml. of enriched Albimi brucella broth in accordance with the Castaneda procedure.[2]
4. A screw-cap tube containing 20 ml. distilled water.

This study was supported in part by a research grant from Eli Lilly and Company, Indianapolis, Ind.

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The three media receiving whole blood were incubated at 36.5°C. in an atmosphere of 10 per cent carbon dioxide. They were subcultured onto enriched Albimi's brucella agar on the third, sixth, ninth, fourteenth, and twenty-first days of incubation. The blood lysed in distilled water was centrifuged at 3,000 r.p.m. for 30 minutes and the supernatant was discarded. One-tenth milliliter aliquots of the remaining blood sediment were inoculated onto enriched Albimi's brucella agar, human blood agar, and chocolate agar, all of which were incubated in an atmosphere of 10 per cent carbon dioxide. One-tenth milliliter of the blood sediment was inoculated into thioglycollate broth (Difco). Subcultures from the thioglycollate broth were made as above and incubated under anaerobic conditions.

In 55 patients only a single blood culture was made; in 10 patients from two to three cultures were obtained; and in 35 a series of eight blood cultures was examined. In the latter group, four cultures were taken on a single day at two-hour intervals and four additional cultures were obtained daily for four days. Among the normal individuals not seeking medical care, 10 were cultured once per day for five days, and six were cultured on two days. The remaining 34 normal persons were admitted to the Veteran's Administration Hospital for simple herniorrhaphy only, and suffered from no other recognizable disease. Of this group, 15 were cultured on the days before and after operation, and 19 were cultured only on the day prior to operation.

Colonial morphology was determined following 48 hours of incubation of the UPB on enriched Albimi's brucella agar. A dissecting microscope (x30) and obliquely transmitted light were employed in all observations.

RESULTS

Unidentified pleomorphic bacteria were isolated from 8 of 35 patients with a clinical diagnosis of fever of unknown origin, from 10 of 23 patients with syndromes including Hodgkin's disease, lymphogenous and myelogenous leukemia, and lymphosarcoma, from 10 of 13 patients with chronic brucellosis, from 5 of 8 patients with cardiovascular disease, and from 2 patients with Reiter's disease. The remaining seven strains were recovered from the blood cultures of 19 patients suffering from miscellaneous types of disease, including metastatic cancer, Marie Strumpell's syndrome, aplastic anemia, meningitis, encephalitis, infectious myocarditis, pulmonary emphysema, and chronic thrombophlebitis (Table I). Two strains of UBP were isolated from the group of 50 normal individuals; one from a nonhospitalized person, and one from a patient admitted for herniorrhaphy. The microorganisms which were isolated in association with the UPB in cases in which two or more organisms were isolated are presented in Table II. The types of bacteria isolated from blood cultures in the absence of UPB are presented in Table III.

Microscopically, unidentified pleomorphic bacteria exhibit a marked degree of pleomorphism. Many strains resemble Corynebacteria showing club forms and palisading. A number of bizarre forms may be present, together with small and large rods. Bipolar swellings, bars and granules, coccoid and coccobacillary forms, rings and granules are typical (Fig. 1). The average length

TABLE I. ISOLATION OF UNIDENTIFIED PLEOMORPHIC BACTERIA FROM BLOOD CULTURES ON 100 PATIENTS WITH CHRONIC ILLNESS AND ON 50 NORMAL PERSONS

CLINICAL DIAGNOSIS	PATIENTS (NO.)	BACTERIA ISOLATED (NO.)				CULTURES NEGATIVE (NO.)
		UPB ONLY	UPB AND OTHER BACTERIA	TOTAL UPB	OTHER BACTERIA ONLY	
Fever of Unknown Origin	35	4	4	8	12	15
Leukemia and Lymphoma	23	8	2	10	1	12
Brucellosis (Chronic)	13	7	3	10	0	3
Cardiovascular Disease	8	1	4	5	2	1
Reiter's Disease	2	2	0	2	0	0
Miscellaneous	19	2	7	9	1	9
Normal Controls	50	2	0	2	0	48
Total	150	26	20	46	16	88

TABLE II. BACTERIA ISOLATED WITH UPB FROM BLOOD CULTURES

CLINICAL DIAGNOSIS	PATIENTS	BACTERIA ISOLATED*				
		STAPHYLOCOCCUS	BRUCELLA	GAMMA STREPTOCOCCUS	ALPHA STREPTOCOCCUS	UNIDENTIFIED GRAM-NEGATIVE COCCI
Fever of Unknown Origin	4	4			1	
Leukemia and Lymphoma	2	1				
Chronic Brucellosis	3	3	2			
Cardiovascular Disease	4	2		1		1
Miscellaneous	7	7				

*More than one species of microorganism was isolated from a few patients in addition to UPB.

TABLE III. BACTERIA ISOLATED FROM BLOOD CULTURES NOT YIELDING UPB

CLINICAL DIAGNOSIS	PATIENTS	BACTERIA ISOLATED*			
		STAPHYLOCOCCUS	GAMMA STREPTOCOCCUS	ALPHA STREPTOCOCCUS	BACTEROIDES
Fever of Unknown Origin	12	10	1	2	1
Leukemia and Lymphoma	1	1			
Cardiovascular Disease	2	2			
Miscellaneous	1	1			

*More than one species was isolated from a few patients.

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of the rods is 3 microns, while the coccal forms average 1 micron in diameter. The Gram reaction is variable; however, the rod forms tend to be predominantly Gram positive. Spores, capsules, and flagella are absent.

A typical 48-hour colony varies from 0.1 to 0.3 mm. in diameter, is round, with an entire or undulate edge. The surface is finely granular with an elevated periphery and a papillate central portion. The colonies, by reflected light,

Fig. 1.—Gram stain of a typical strain of UPB. (Approximate magnification ×2,000.)

are light cream in color, and have a darker brown center. By obliquely transmitted light, they are opalescent with a bluish-white cast (Figs. 2 and 3). Broth cultures exhibit either a uniform turbidity or a granular growth which settles to the bottom of the culture tube. Hemolysis has not been observed on human or rabbit blood agar. Thirteen strains were resistant to penicillin, nine to streptomycin, two to Aureomycin, none to Achromycin, and one each to Terramycin and erythromycin.

The UPB have not, to date, produced observable disease in mice, rats, hamsters, guinea pigs, and rabbits. Furthermore, the organisms have not been recovered from their blood or tissues at autopsy. All strains, however, were pathogenic for five-day chick embryos, and caused death in from 1 to 14 days. UPB were recovered from the yolk sac of infected embryos at the time of death, but in no case could they be recovered from normal embryos used as controls.

DISCUSSION

In view of the marked morphologic similarity of the UPB to certain species of Corynebacteria, taxonomically they might be placed in this genus. Fleisher[3] has described similar organisms which he isolated from patients with diseases of the lymphatic system, particularly Hodgkin's disease. It is interesting to note that a striking parallel exists between the principal sources of Fleisher's

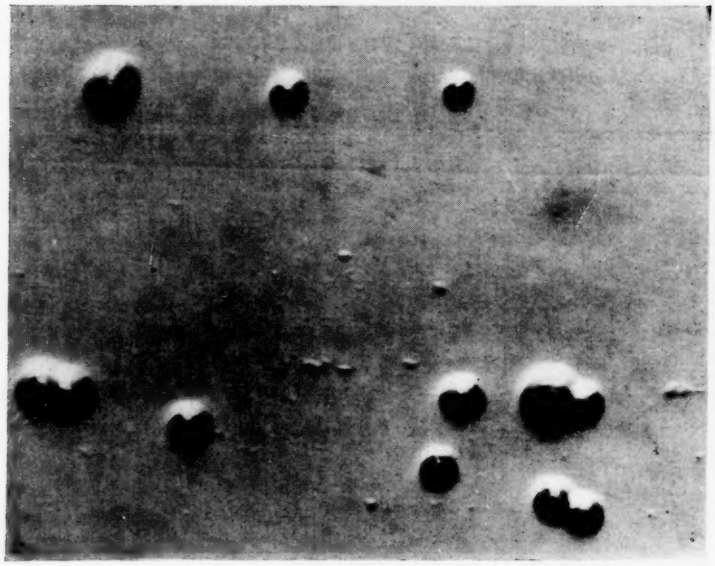

Fig. 2.—Colonies of UPB on the surface of agar; 48 hours' incubation at 36.5°C. (Approximate magnification ×30.)

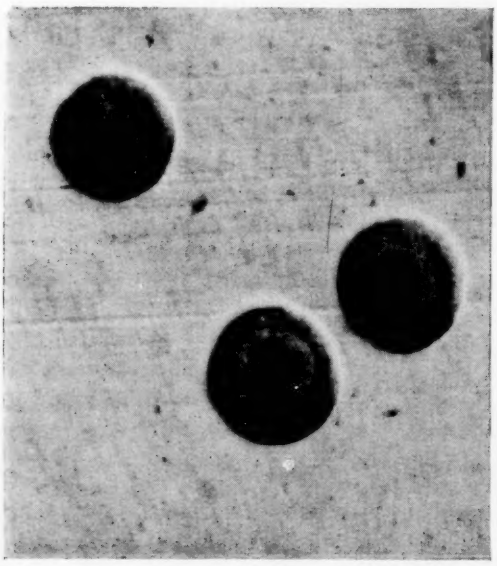

Fig. 3.—Colonies of UPB on the surface of agar plate. Forty-eight hours' incubation at 36.5°C. Enlargement of Fig. 2. (Approximate magnification ×90.)

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strains and those from which the UPB were obtained. In both studies the majority of strains were recovered from patients with fevers of undetermined origin and from such chronic illnesses as Hodgkin's disease, leukemia, and malignant lymphoma.

Although UPB were isolated from two apparently normal individuals, they were recovered from the blood of 44 per cent of the patients with chronic illness. The consistency with which they were isolated leaves little doubt that UPB are present in the blood and tissues of certain patients with chronic illness. Although no etiologic relationship of UPB to disease has as yet been established, a number of possibilities should be considered. A causal relationship between UPB and chronic disease is possible. Such bacteria may represent opportunists or secondary invaders which become established in a host with a deranged physiologic state.

This report serves to call attention to a group of microorganisms which appear to have significance in chronic disease, yet their role in prolonged illness cannot be properly evaluated until further studies have been carried out.

SUMMARY

1. Unidentified pleomorphic bacteria were isolated from the blood of 44 of 100 patients with chronic illness including fevers of unknown origin, lymphomas, chronic brucellosis, cardiovascular disease, and Reiter's disease. In only two instances were similar organisms isolated from so-called normal individuals.

2. A number of the UPB were resistant to penicillin and a few were resistant to other antibiotics.

3. The organisms are morphologically very similar to Corynebacteria and may belong to this genus.

4. None of the UPB were pathogenic for laboratory animals. All, however, were pathogenic for five-day chick embryos.

We are grateful to Doris M. Monroe, B.S., for technical assistance.

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A HOSPITAL UNIT FOR THE CARE OF THE PATIENT WITH LONG-TERM ILLNESS: THE INTERMEDIATE SERVICE

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WHILE the literature pertaining to the problems arising from increased longevity has become voluminous, there is a relative paucity of articles concerned with what appears to be the crux of the problem from the standpoint of institutional care—the care of the patient with long-term illness. The factor of age has importance primarily in that with advancing age comes a higher incidence of long-term illness and infirmity. Roberts[1] has recently pointed out that approximately 8 per cent of our total population is 65 years of age or over, yet this age group accounts for 40 per cent of those with long-term illness.

Bluestone[2] has raised some very pertinent questions: "What shall we recommend as an acceptable standard in the institutional care of the aged, with particular respect to medical care? Is it possible to give complete, comprehensive and continuous medical care within an institution which is not geared to full hospital service? If not, what shall we recommend as a plan of complete or partial integration by which the home for the normal aged can be supported, wherever required, by the collaboration of the general hospital? How far shall we permit an infirmary within an institution for the aged to go in medical care?" These questions are considered applicable to the problem of care for the patient with long-term illness, irrespective of age.

The European literature contains numerous articles concerning coordinated and integrated programs for the institutional phase of the care of the geriatric and chronic patient. Elliott[3] has pointed out that England has an even higher percentage of old people than the United States, 10.8 per cent over 65 years of age as compared to 8.5 per cent. The problems related to increased longevity appeared in Europe several decades before they reached corresponding proportions in this country. This factor, and others concerned with economics and medical practice, apparently account for the advanced planning and coordinated effort toward solving these problems, particularly in England and the Scandinavian countries. Elliott described three basic units: (1) an active geriatric unit comprising a ward in a general hospital, (2) an annex of the hospi-

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tal for continued treatment of long-term patients transferred from the acute hospital, and (3) the Halfway House for the frail ambulant halfway between hospital and home.

Brooke,[4] in elaborating on the Halfway Houses, has described an approach which is gaining in application. He says: "A solution for the infirm old people, wrongly occupying hospital beds and unsuitable for old age homes, is to be found in what are often known as 'Halfway Houses' where old people, frail but not wholly bedfast, can receive adequate care. Medically they would still be under the supervision of the hospitals' physicians and they could be readily readmitted to the hospital when need arose."

Roberts[5] has emphasized that the needs of the long-term patient are more complicated than those of the acutely sick person. "He may have a multiplicity of serious diseases. He is in need of intensive diagnostic study and evaluation—his total adjustment to life may be seriously disturbed—extensive services are required to provide for the medical, nursing, emotional, spiritual, economic, social and rehabilitative aspects of his care. The patient's general condition is rarely static and is subject to continual change, requiring extensive health and institutional resources. In planning services for the chronically ill, therefore, we must keep paramount at all times the requirement that all the services needed are tied in together sufficiently closely so that they are readily available to the patient when they are needed. To some, such close coordination can be achieved only if all services are provided by a single institution. To others, close administrative relationship of separate physical facilities will do the trick."

PROBLEM OF LONG-TERM ILLNESS IN THE VETERAN POPULATION

The Veterans Administration, in carrying out its responsibility under Congressional Acts prescribing medical care for veterans, is faced with the same problem that confronts the nation in providing for the needs of the geriatric patient and the patient with long-term illness, on an effective yet economical basis. Medical advances have materially aided in the solution of the problem for the tuberculous patient, and the peak of the load may have been reached. Great strides have been made and extensive facilities provided for coping with the problem as it relates to the psychiatric patient. The growing and pressing need which is becoming more acutely evident as the Veteran population ages (the average age of the World War I veteran is now 60.4) is the need for hospital bed units for the care of the patient with long-term illness in the medical, surgical, and neurological categories.

VETERANS ADMINISTRATION CENTERS

The Veterans Administration Center at Kecoughtan, Virginia, on the shores of Hampton Roads, comprises a 570-bed general medical and surgical hospital and a 1,303-bed domiciliary home. The Veterans Administration operates fourteen centers of this type, having a total domiciliary bed capacity

of 15,874 and three other separate domiciliary units having an additional capacity of 1,892 beds.

The admission criteria to the domiciliary units explain in large measure the predominance of chronic disease and long-term illness at these centers. The veteran must meet certain medical and legal criteria for admission to either the hospital or the domiciliary section. The following which is quoted from the regulations governing medical eligibility for admission to the domiciliary section imposes the requirement of chronic disability, ". . . a disability, disease or defect . . . which . . . is producing disablement of such degree and of such probable persistency as will incapacitate from earning a living for a prospective period. . . ."

Barrett and his associates[6] analyzed the chronic disease problem at a Veterans Administration Center and indicated the age level of patients and the incidence of the most common diagnostic categories. The mean age of the domiciliary patient was found to be 61, with 53 per cent in the age group of 55 to 64, while only 4 per cent were under 45, and 9 per cent over 75. Analysis of the morbidity of the domiciliary population revealed that diseases of the circulatory system were the most common, diseases of the nervous system and sense organs were next in order, and diseases of the musculoskeletal and respiratory system ranked third and fourth. A similar study carried out at this Center indicates essentially the same figures for age levels and morbidity.

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DESCRIPTION OF THE INTERMEDIATE SERVICE UNIT

It is the purpose of this paper to discuss in some detail a special hospital unit established at this Center to provide total care for the long-term patient whose disabilities are of such degree as to be unmanageable in the domiciliary section, yet not requiring the facilities of the acute general hospital. Such a unit may be referred to as the chronic hospital, convalescent hospital, or nursing home section at various centers, but we chose the term, intermediate service unit, as more appropriate to its functional position between our other general hospital services and the domiciliary section and because the term avoids the connotation of finality.

Facilities.—The unit was established through conversion of a 150-bed domiciliary barracks to a 100-bed hospital unit and was placed in operation Nov. 30, 1953. Rather than a description of these improvised facilities, we wish to emphasize certain principles of design that our experience has indicated are of vital importance in planning a unit for the care of the long-term patient. First, the basic design of such a unit should locate the bed sections as small wings, preferably on one floor, radiating from a central area. All of the special facilities pertaining to the supervised activities and treatment program should be located within the central area of the unit in order to minimize the problem of transportation of severely disabled patients and to enhance the motivating force of the general activities program. Second, particular attention must be given to the design of the structure and its equipment with a view to minimizing hazards for the disabled and infirm patient and to the application of specially adapted equipment for bathing, feeding, and simplifying the management of

the ordinary activities of daily living for the handicapped person. Third, emphasis must be placed on making the unit homelike and livable, eliminating insofar as possible the usual hospital atmosphere, though containing all essentials for complete nursing care. Finally, the requirement for space per bed and for the activities and treatment center is much greater than is provided by the standards that are ordinarily applied to general hospital wards and most chronic hospitals that have been constructed. It must be appreciated that the patient's bed area may be his home as well as his hospital bed for long periods of time.

PERSONNEL REQUIREMENTS

Physician.—We have found that one full-time physician can adequately supervise the care of 100 patients in this unit. This compares with the usual ratio of 1 doctor to 30 patients on the acute medical wards of the main hospital.

Nursing Service.—In planning the nursing staff for this unit it was believed that a minimum of full-time professional nurses would be required with a higher ratio of hospital aides to nurses than the usual ratio for acute hospital wards. An analysis of the patient-nursing service personnel ratios for this unit as compared with the ratios for the acute general medical and surgical services is shown in Table I.

TABLE I. NURSING SERVICE PERSONNEL ON INTERMEDIATE SERVICE AS COMPARED TO GENERAL MEDICAL AND SURGICAL SERVICES*

Patient-nurse ratio, G.M. & S. Services	5.4
Patient-nurse ratio, Intermediate Service	13.3
Patient-practical nurse ratio, G.M. & S. Services	57
Patient-practical nurse ratio, Intermediate Service	100
Patient-hospital aide ratio, G.M. & S. Services	4.9
Patient-hospital aide ratio, Intermediate Service	5.3

*These ratios include all personnel assigned, exclusive of supervisors, and *do* allow for days off, sick leave, and annual leave.

There are 13.3 patients per professional nurse on the intermediate service as compared with 5.3 patients per nurse on the other general medical and surgical services, or approximately 2½ times as many patients per nurse. There are too few practical nurses for a significant comparison. The patient-hospital aide ratios are not significantly different for the acute and intermediate services.

Table II shows the assignment schedule for nursing personnel. In addition to the scheduled assignments as shown in the table, the nursing supervisor for the neuropsychiatric service also provides general supervision of the intermediate service. Similarly, staff nurse coverage during the period from 12:00 midnight to 8:00 A.M. is provided by a nurse on call from the near-by closed ward section of the neuropsychiatric service.

TABLE II. SCHEDULE OF NURSING PERSONNEL

Ward 5	*Capacity: 33*
7:45 A.M. to 4:30 P.M.	head nurse (½)
6:45 A.M. to 3:30 P.M.	1 nurse
	2 aides
7:45 A.M. to 4:30 P.M.	½ practical nurse
10:15 A.M. to 7:00 P.M.	1 aide
3:15 P.M. to 12:00 midnight	½ nurse
	1 aide
12:00 midnight to 8:00 A.M.	1 aide
Ward 6	*Capacity: 67*
7:45 A.M. to 4:30 P.M.	head nurse (½)
6:45 A.M. to 3:30 P.M.	1 nurse
	3 aides
7:45 A.M. to 4:30 P.M.	½ practical nurse
10:15 A.M. to 7:00 P.M.	1 aide
3:15 P.M. to 12:00 midnight	½ nurse
	1 aide
12:00 midnight to 8:00 A.M.	1 aide

Ancillary Personnel.—The supporting cast of professional and subprofessional workers needed to complete the team includes therapists from all sections of the Physical Medicine and Rehabilitation Service; i.e., physical therapy, corrective therapy, and occupational therapy; clinical psychologist, social worker, the chaplains in all faiths, special service representatives in recreation, library service, and, most important, the volunteers. This array of professional and subprofessional talent required to provide total care to its full extent can be provided on a practical basis for a unit of this size only through an integral relationship with a completely staffed general hospital or medical center. In addition, consultation services in most specialties must be readily available from the full-time or consultant staff of the acute hospital.

ADMISSION CRITERIA

The following are the criteria for admission to the intermediate service unit:

1. Patients are admitted by transfer from the other clinical services of the hospital or from the domiciliary section of the center. No direct admissions from the outside are accepted.

2. All patients admitted must have had complete diagnostic studies and all definitive measures of treatment considered possible completed before referral for transfer.

3. Patients must be able to feed themselves with a minimum of help and be physically able to get to the near-by dining hall, with help in a wheel chair if necessary, because of the limitation of diet facilities of the unit now in operation.

4. Patients must not be mentally confused or deteriorated to the extent that constant supervision is required.

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5. Patients must be free of communicable diseases.

6. All patients referred for transfer are screened by the Center's Rehabilitation Board to determine: (a) that all admission criteria are met; (b) that there is no other feasible disposition of the patient, such as discharge to his own home or nursing home or to the domiciliary section and; (c) that the requirements for care can be met by the facilities and personnel of the unit.

MEDICAL EVALUATION

Regardless of the extent of previous medical evaluation, the medical history is reviewed and a complete physical examination is done by the physician assigned to the unit and such laboratory work repeated or accomplished as deemed indicated.

Standard hospital records are maintained. Each patient is reviewed either before or immediately after transfer to the intermediate wards by the Chief of the Physical Medicine and Rehabilitation Service. He consults with the patient's ward physician with regard to the patient's special rehabilitation program and evaluates his abilities as regards the activities of daily living. The accomplishment and maintenance of these functions is the minimum goal for all patients. A self-care bed tag, reproduced as Fig. 1, is used as a means of constantly focusing the attention of all members of the medical team on these objectives.

SELF-CARE BED TAG

Can perform.....blue
Work toward.....red
.....Early morning care.
.....Use toilet alone.
.....Dress self.
.....Shave.
.....Bathe.
.....Walk alone.
.....Wheel self to meals.
.....Feed self.

SPECIAL CONSIDERATIONS:

Name Ward

Fig. 1.—Self-care bed tag.

DIAGNOSTIC CATEGORIES

The classification of patients by diagnostic categories on the wards of the intermediate service as of Nov. 30, 1953 (Table III) is presented to illustrate the wide variety of clinical conditions represented.

The individual diagnostic categories listed are not to be interpreted as the sole basis for the patient's admission to the unit. As a matter of fact, the majority of patients with long-term illness, particularly in the old age group, have a combination of three or more of the conditions shown; and it is the resultant disability plus social, psychologic, and economic factors that determines the

TABLE III. CLASSIFICATION OF PATIENTS BY DIAGNOSTIC CATEGORIES AS OF NOV. 30, 1954

Medical	
C. V. D.*	16
Diabetes	6
Emphysema	10
Asthma	2
Arthritis	2
General A.S.†	13
	49
Neurological	
Hemiplegia	14
Trans. myelitis	1
Multiple sclerosis	2
Cerebral A.S.†	3
C.N.S. syphilis	3
Thrombosis ant. spinal artery	1
	24
Surgical	
Cataracts	1
Amputation	1
Fractured hip	1
Cancer of lung	2
Cancer of pharynx	1
Cancer of larynx	1
Ulcer of feet	1
Hypertrophy of prostate	1
Fistula-in-ano	1
Trophic ulcer of foot	1
Decubitus ulcer	1
Cellulitis of legs	1
	13
Psychiatric	
Paranoid personality	
Chr. brain syndrome associated with cerebral A.S.†	6
Schizophrenic reaction	3
Psychoneurotic disorders	2
	12

*Cardiovascular disease.
†Arteriosclerosis.

eligibility and need for care on a unit of this type. It is desired to emphasize, also, that patients are not grouped within the ward under any particular diagnostic category, and a definite effort is made to avoid the stigma of a diagnostic tag. While the physician and the records concern themselves with the particular clinical conditions requiring observation and treatment as such, the staff's primary concern is with the patient as a whole human being and his rehabilitation goal. In working with the patient with long-term illness, particularly in the older age group, it becomes evident that the condition or conditions which have been the focus of attention for diagnosis and treatment during his stay in the acute hospital become incidents of varying importance with respect to the individual patient's total living experience. Frequently the major pathologic process which may be expected to result ultimately in the patient's death is of a great deal less concern to the patient and less disturbing to his adjustment to living than other more minor physiologic and psychologic derangements. For example, the patient may have adjusted to the acceptance of the miseries of a crippling arthritis, of the results of advanced peripheral vascular disease, or even of a progressing malignant process, but be quite disturbed and maladjusted because of such petty annoyances as ill-fitting dentures or an incompatible relationship with a neighboring patient.

The group of psychiatric patients listed in this table is worthy of special comment. The ten patients diagnosed as psychotic had been confined to the closed ward of the hospital for periods ranging from two and a half weeks to twenty-one months. They were all considered in the "burned-out" nonaggressive stage, having considerable deterioration and at times manifesting some degree of confusion and disorientation. These patients were accepted in transfer

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on the assumption that the unit would provide a sufficiently protective environment for their care. The response of these patients to a more tranquil, less threatening and more homelike environment than can be provided on the acute closed psychiatric ward has been remarkably good. Bartfield[7] described dramatically the effectiveness of the principle of treating mental illness with friendship at the Motivation Clinic of the Veterans Administration (Brentwood) Hospital, Los Angeles, where the emphasis is not on methods, but on the rapport established between the clinic personnel and the patients. Donahue and associates[8] have reported a movement in Europe toward transfer of psychotic patients who have reached the regressed, nonaggressive stage out of mental institutions to foster homes, nursing homes, and other types of chronic care units. On the intermediate service these patients are managed on the same basis as the nonpsychotics, subject to the same daily routines and the same friendly attitudes and efforts on the part of the staff to encourage participation in the varied activities program.

ATTITUDES AND RESPONSIBILITIES OF PROFESSIONAL STAFF

Our experience has indicated that the key to the successful accomplishment of the mission of a hospital unit for the care of the patient with long-term illness is the spirit, enthusiasm, morale, and teamwork of the staff. Careful selection of the key members, the doctor, nurse supervisor, and head nurses, with particular reference to personalities, humanitarian interests, degree of optimism, and team spirit is the first essential. Previous experience in the care of this type of patient is of course an asset, but is less vital than the aforementioned qualities.

The attitude of management is the second vital force. This must be one of understanding and support that will impart proper stature and recognition to the program through emphasis on quality of personnel, facilities, equipment, and effectiveness of performance on a comparable level to the other professional programs of the hospital or station.

The third prerequisite is a program of thorough orientation and special training for all personnel assigned.

ROLES OF KEY PERSONNEL

The *physician* in charge should be one who has had a broad professional experience as a general practitioner or internist. He must be possessed of a well-balanced combination of both the art and the science of medicine. He must have a congenial and sociable personality with a strong humanitarian urge. He must be a good team leader able to inspire others with a sense of optimism in working with patients generally regarded as having a poor or even hopeless prognosis. He must be constantly alert to the importance of anticipation as a therapeutic objective, in the sense so aptly described by Stieglitz.[9] He should be ever alert to the first warnings of impending heart failure, peripheral circulatory failure, infections, renal and neurologic complications, and for a change in the patient's symptoms and signs suggesting the development

of a complication or a new condition. Many catastrophies that often develop insidiously in the elderly patient can be forestalled or prevented if anticipated and actively treated at or before the onset.

The *nurses* must be imbued with a spirit of service, kindliness, patience, and an appreciation that the small things are of tremendous importance in the life of the patient with long-term illness.

The *physical medicine and rehabilitation staff* plays a very important role. The physiatrist must have a broad perspective toward rehabilitation and an appreciation of the values that all the modalities of treatment, physical therapy, occupational therapy, and corrective (exercise) therapy have in tonic effect and preventive maintenance benefit as well as for their specific functional objectives. The therapists must be so oriented as to gain satisfaction from observing the benefits of increased well-being, mental alertness, reawakening of an interest in life, and increased socialization. Although specifically prescribed for the individual patient, these modalities of treatment should be located and scheduled so as to be an integral part of the planned activities program.

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The *clinical psychologist* is an essential member of the team. It is recognized that an understanding of the personality factors in the long-term patient is a prerequisite to helping him make an optimal adjustment. In the intermediate service unit the psychologist contributes effectively to the diagnostic and therapeutic program and also serves in an advisory capacity to the staff in the interpretation of group dynamics and other unique psychologic problems which arise in a unit such as this.

Social service is the fourth basic element of the team. Experience has already shown the staff that regardless of the extent of previous social study and contacts, further progress can often be made, with renewed effort and persistence, toward the goal of re-establishment of family and community contacts leading to reintegration of the patient into his home environment.

A recent social service survey of all patients in the intermediate unit brought to light certain characteristic sociologic data. The majority of the patients are World War I veterans (77 per cent) as compared with Spanish American War (14 per cent) and World War II (10 per cent). The patient's average age is 62. He is most likely widowed, single, separated or divorced (77 per cent) rather than married (23 per cent). He is receiving some sort of pension (75 per cent receive from $63.00 to $129.00 per month). Approximately 20 per cent are considered incompetent to handle their own funds. Loose family ties are common; a sister (35 per cent) or wife (23 per cent) are usually given as nearest of kin. Contact with family or friends through correspondence is maintained weekly or monthly (62 per cent) and is negligible for 25 per cent. The most startling revelation of this study of family ties was the fact that 37 per cent had no personal contact from relatives or friends from the time of admission to the center.

A major objective of this study was to determine the social discharge potentials of those patients considered medically feasible for care in their own homes or in nursing homes. The findings indicated that discharge planning could be considered favorable for 15 per cent, possible for 10 per cent, and unfavorable for the remaining 75 per cent.

Special service is the fifth element of the team. This service has several important components: (1) library service, (2) recreation program, and (3) volunteer program. The role of each can readily be deduced from the emphasis that is placed on a dynamic activities program.

Chaplain service is last, but not least. As we have already indicated, the responsibility of the medical team caring for the long-term patient must be for the whole man. This objective cannot be fulfilled without giving appropriate attention to his spiritual needs.

ACTIVITIES PROGRAM

Table IV shows the time schedule of activities for patients.

TABLE IV. SCHEDULED ACTIVITIES FOR PATIENTS

TIME	ACTIVITY
DAILY ACTIVITIES*	
5:30– 7:00 A.M.	Lights on—morning care
7:15– 9:00 A.M.	Breakfast (in 2 groups)
8:00– 9:00 A.M.	Ward physicians rounds
9:00–12:00 noon	Corrective therapy; blind therapy; occupational therapy; physical therapy
12:15– 2:00 P.M.	Dinner (in 2 groups)
2:00– 4:00 P.M.	Occupational therapy; corrective therapy
5:15– 7:00 P.M.	Supper (in 2 groups)
9:30 P.M.	Lights out
WEEKLY ACTIVITIES	
Sunday— 9:15 A.M.	Church services
Monday— 9:00–11:00 A.M.	Games and music
7:15– 9:00 P.M.	Bingo
Tuesday— 7:15– 9:00 P.M.	Rhythm band (patients)
	Recreational games
Wednesday—9:00–11:00 A.M.	Recreation games
7:15– 9:00 P.M.	35 mm. slides
Thursday— 2:00– 4:00 P.M.	Table games
7:15– 9:00 P.M.	Recreational games and social contact (10 volunteers)
Friday— 9:00–11:00 A.M.	Grand rounds
7:15– 9:00 P.M.	Games
Saturday— 2:00– 4:00 P.M.	Letter writing
	Movies (16 mm.)
MONTHLY ACTIVITIES	
1st, 3rd, 4th Tuesday—2:00–4:00 P.M.	Movies (16 mm.)
2nd Tuesday—2:00–4:00 P.M.	Birthday party
1st and 3rd Thursday—2:00 P.M.	Recreational council (6 patients on council)

*Times are not shown for medications, nurses rounds, special visits by social worker, psychologist, special service representatives, and the chaplain; or for referral to clinics and consultants.

Experience with the program has indicated that certain principles pertaining to the varied activities deserve emphasis:

1. All activities must be planned for smooth integration into the patients' daily routines, allowing for many variables to fit the wide range of disabilities and personalities. This requires close teamwork to carry on simultaneously many activities of both a passive and active variety.

2. The most effective activities from the standpoint of motivation are those in which the patient actively participates and assumes some of the initiative. To obtain more active patient participation we have encouraged small patient groups to function as committees to participate in planning and lend inspiration to others.

3. Full advantage should be taken of the volunteer as a link between the patient and life in the community for this is the volunteer's most valuable potential. The volunteer is also, of course, identified with many personal services, augmenting or supplementing the medical program. Care should be exercised to adequately supervise, instruct, and coordinate the volunteers' activities so that the optimum in patient response will result.

4. The most difficult problem is motivation of the patient to accept and participate in the planned activities. We have found that this is facilitated by having all possible activities take place in suitable space within the unit where they may be frequently observed and accepted by the patient as a part of the daily routine. Even the most resistant patient eventually responds to continuous stimulation, example, and encouragement.

5. The multiplicity of activities taking place simultaneously in a single area may give the impression to the casual observer of confusion and at times of bedlam, particularly when the rhythm band is in full swing. Experience has convinced us that this has a desirable tonic and motivating effect on the majority of long-term patients, for only rarely does a patient manifest a determination to withdraw to peace and solitude, except during episodes of indisposition. In this regard these patients appear to enjoy the group commotion much as do children, either as participants or spectators.

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GENERAL STAFF MEETINGS

Essential to the planning, coordination, and inspiration of a dynamic program of the type described are regularly scheduled general staff meetings with all members of the team represented. The physician, as the team leader, acts as chairman, and minutes are recorded, but emphasis is on informality and a free discussion of all problems and ideas. It must be recognized that in a dynamic program there will be change, and there must be opportunity to explore all avenues of approach.

OPPORTUNITIES FOR RESEARCH

The opportunities for research and clinical investigation presented by a coordinated and controlled program for the care of the long-term patient of the type described are manifold.

In the field of clinical psychology there is great need for well-designed studies to measure the effects of the type of program described. For example, Moreno's sociometric technique as applied by Donahue and associates[10] to measure the effectiveness of an activity program appears appropriate to study further the gains which have become subjectively apparent to the staff. The psychologist faces a major challenge in adapting his armamentarium of psychodiagnostic instruments to the effective study of the aged, long-term patient or to devise new instruments to study this selected group.

There is presented an unusual opportunity to observe under scientific conditions the process of aging and the relationship thereto of nutritional and endocrine factors, and an excellent opportunity to observe the effect of minimizing the factor of stress.

There is opportunity to develop further the basic principles of care for the long-term patient, the techniques, and the means by which the whole problem can be integrated at its proper plane in the sphere of medical and hospital practice.

In the interest of progress in this complex and challenging field of chronic disease it is hoped that the presentation of this paper will stimulate others to suggest or carry out studies that such a unit makes possible.

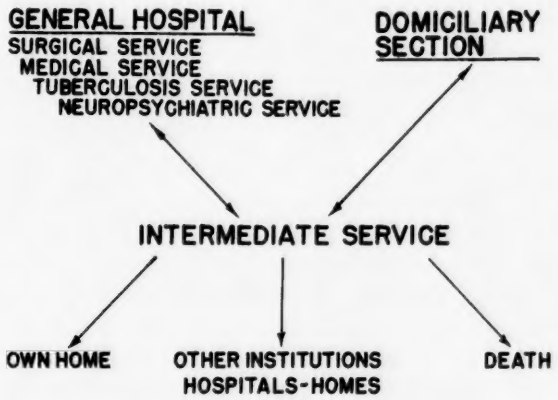

Fig. 2.—Flow of patients.

RESULTS

We have thus far observed some positive results which are listed in the following paragraphs.

1. *Patient Turnover.*—As the title, intermediate service, implies, the patient population of such a unit is not static.

The direction of flow of patients to and from the intermediate service is shown in Fig. 2. The arrows indicate a movement of patients back and forth between the intermediate service and the other clinical services of the hospital and the domiciliary section of the center. These transfers are based on the patient's treatment requirements at the time. The other dispositions are indicated by arrows pointing in one direction only, as no direct admissions or readmissions from outside the center are accepted. A patient discharged to home or another institution must be readmitted to the appropriate clinical service of the acute hospital for re-evaluation before transfer to the intermediate service.

It is to be expected that a fairly large percentage of the patients on an intermediate service of this type will ultimately require transfer to the acute hospital. This is because of the inevitable development of complications, progression of basic irreversible disease, or development of acute intercurrent conditions increasing requirements for care beyond the capacity of the unit.

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TABLE V. GAINS AND LOSSES FOR PERIOD JUNE 30, 1954, TO DEC. 31, 1954

	NUMBER	% OF TOTAL	
Gains			
From domiciliary	20	26	
From acute hospital	48	62	
From other V. A. hospitals	4	5	
From closed psychiatric ward	5	7	
Total	77	100	
Losses			
To acute hospital	33	47	
Irregular discharge	2	3	
Died	3	4	
Discharged home (To self-care)	8	11	46%
To Domiciliary (To self-care)	25	35	
Total	71	100	

Table V, showing the gains and losses for the last six-month period of operation, indicates that 33 patients (47 per cent of those discharged) were transferred to the acute hospital. Of these, approximately 46 per cent were for terminal illness, 27 per cent because of acute exacerbations or intercurrent illness (these subsequently returned to the intermediate service) and 27 per cent are still residents on the wards of the acute hospital as of the writing of this report.

Of greater significance, the table indicates that a dynamic program as described increases motivation and enhances rehabilitation to the extent that a significant number of long-term patients on the wards of the intermediate service achieve a level of stability and self-sufficiency that makes feasible their discharge to their own homes or to the domiciliary section of the center. It will be noted that 25 (35 per cent) have been discharged to the domiciliary section and 8 (11 per cent) to their own homes, a total of 46 per cent who may be considered as having been discharged to self care. This result indicates

that despite a poor prognosis there remains for a large number of chronic patients a significant rehabilitation potential.

2. *Ambulation of Wheel-Chair Patients.*—As further evidence that a rehabilitation potential exists for chronic patients, we submit the accomplishments for wheel-chair patient shown in Table VI. This table is divided into two groups: those who are now completely ambulant and have discarded their wheel chairs, and those who are partially ambulant, still needing their wheel chairs at various times.

TABLE VI. AMBULATION OF WHEEL-CHAIR PATIENTS

COMPLETELY AMBULANT		PARTIALLY AMBULANT	
NO. OF PATIENTS	TIME IN WHEEL CHAIR (YR.)	NO. OF PATIENTS	TIME IN WHEEL CHAIR (YR.)
3	Less than 1	2	1
2	2	2	3
2	3	3	4
1	6	1	5
		2	8
		1	18

The duration in years which these patients had spent confined to wheel chairs is shown for the patients in each group. While the corrective therapists play the key technical role in this accomplishment, the great importance of the motivating force of the total program is indicated by the fact that the majority of these patients had previously had available to them all of the usual modalities of treatment designed to promote ambulation. The importance to the morale of the patient and to reduction of back-breaking workload on nursing personnel of even partial ambulation should not be underestimated.

3. *Psychologic Benefits.*—The most striking results, as previously inferred, are psychologic. They are manifested by increased motivation, restoration of dignity, sense of importance and self-respect, renewed hope and interest in life, and acceptance of the philosophy that life can be worth living in spite of chronic infirmity and disability. Another significant collateral benefit in this category is the demonstration that members of a high caliber medical staff can obtain gratifying professional satisfaction as result of their efforts and accomplishments for the type of patients who are frequently the forgotten men, the discards, often disrespectfully referred to as "bed freezers" on acute hospital wards.

4. *Acceptance of the Principles of the Program.*—Finally, the program has been critically reviewed and evaluated by various authorities concerned with the problem of care for the long-term patient. As a result of their enthusiastic endorsement and our recommendations, the Veterans Administration Central Office has authorized the designation of the program at this center as a separate clinical service to be entitled the "Intermediate Service" and to be conducted on a comparable level professionally and administratively with the other clinical services. Approval has also been given to expand further the scope of the

service to include a section for the care of the more severely disabled and non-ambulant long-term patients.

It is significant also that the basic principles underlying the program are essentially those emphasized in the report of the President's Commission on the Health Needs of the Nation as reviewed by Moore and Seegal,[11] in the report of the National Conference of the Commission on Chronic Illness as summarized by Roberts,[12] and by Rusk.[13]

SUMMARY

1. One of the greatest challenges to the medical profession and society today, which paradoxically may be attributed to the advances of medical science, is providing adequately for the result of our increased longevity, the large and increasing number of our population with severely disabling long-term illness.

2. Long-term illness as it exists and is growing in our Veteran population is discussed with particular reference to this problem at the Veterans Administration Center, Kecoughtan, Virginia. The average age of the domiciliary population is 61, corresponding to the average age of World War I veterans (60.4) who comprise the large majority of veterans now resident in domiciliaries. The gamut of conditions in this age group predisposing to chronic disability and long-term illness are present in the domiciliary population.

3. An intermediate hospital unit, designated the Intermediate Service, for the care of the patient with long-term illness, in operation for one year at a Veterans Administration Center, was described. The important features of this unit are: (a) immediate availability of the resources of the acute hospital; (b) informal and homelike environment especially adapted for the care of the long-term patient; (c) emphasis on the team approach and multiple integrated activities.

4. The role of each of the key members of the staff is discussed.

5. An evaluation of the results obtained is gratifying for the measurable accomplishments of increased ambulation of wheel-chair patients and rehabilitation of a surprising number to an extent permitting discharge to their own homes or to the domiciliary section of the center. Psychologic benefits are striking in terms of restoration of hope, dignity, sense of importance, adjustment to disabilities and development of the will to live and make the most of residual capabilities. An additional gratifying result is evidence that sustained interest and enthusiasm of the professional staff in working in the field of chronic disease and long-term illness can be achieved with an approach that gives the program appropriate stature and dignity.

CONCLUSIONS

The establishment of an intermediate service of the type described as an integral part of the professional services of a general hospital gives substance to the proposition of Seegal[14] "that the basic principle in the care of the patient with long-term illness is that he should be treated with the same fidelity and dignity usually accorded the patient with acute illness."

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Review

VASCULAR LESIONS IN DIABETES MELLITUS

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IN THIS review consideration will be given only to those lesions of blood vessels which are characteristic of, or more frequent in, diabetes mellitus. Diseases such as malignant nephrosclerosis, syphilitic arteritis, medionecrosis aortae, polyarteritis nodosa, and thromboangiitis obliterans, which are not known to be more frequent in diabetics than in the general population, will not be considered. Diabetic neuropathy[1] will not be included, since its relation to the vascular disease, if any, is unsettled. The lesions will be discussed primarily from the standpoint of pathology and pathogenesis, with only minor emphasis on clinical diagnosis and treatment. The list of references, while not exhaustive, is intended to include the major contributions, which in turn contain further references for those with special interest in the subject.

The important diseases of the blood vessels in diabetes mellitus are conveniently considered under three headings*:

1. Lesions of the larger arteries (i.e., those usually included under the loosely used term "arteriosclerosis").
2. Lesions of the arterioles, "arteriolosclerosis."
3. Lesions of the capillaries and venules.

Those in groups (1) and (2), while they do not seem to differ qualitatively from the same diseases as seen in nondiabetics, usually occur with greater frequency and severity and often at an earlier age in diabetic patients than in nondiabetics. The lesions in group (3) are so characteristic of diabetes that they may be regarded as almost specific for that disease. This group will therefore be considered later in more detail than the others.

*The use of vague and nonspecific terms, such as "arteriosclerosis" to embrace *all* of the vascular lesions in diabetes, or "vascular nephritis" to include arteriolosclerosis as well as intercapillary glomerulosclerosis, is to be deplored. The lack of correlation between the various types of "arteriosclerosis" was well brought out by the study of Sappington and Cook.[2]

LESIONS OF THE LARGER ARTERIES

These may be considered under three headings: (a) calcification of the media Mönckeberg's sclerosis), (b) diffuse fibrosis of the intima, and (c) atherosclerosis.

Medial Calcification.—Calcification of the media, the Mönckeberg type of sclerosis, is seen characteristically in arteries of the muscular type, particularly those of the extremities in both diabetics and nondiabetics.[3,4] Here it produces the familiar, often palpable "pipestem" type of artery. The calcium salts are deposited in the form of fine granules, apparently chiefly in the connective tissue between the muscle cells, although often within elastic fibers. As the lesion grows, the granules coalesce into a solid plaque which may eventually be transformed into bone. Although fibrous intimal thickening is common, any association with atherosclerosis of the intima seems to be coincidental. In spite of the frequency of palpably thickened radial arteries, atheromatous occlusion of these vessels is almost unknown.[2] There seems to be no correlation of calcification, either medial or intimal, with occlusive disease in the legs.[4a]

The pathogenesis of medial calcification is quite unknown. Something similar can be produced in animals by huge doses of vitamin D or of epinephrine, and it seems probable that a variety of agents may injure the media in such a way as to predispose to calcification. It may occur spontaneously in animals.[3,4]

It is of particular interest that medial calcification of arteries (and even of the vas deferens[5]) is demonstrable by x-ray with great frequency in young diabetics of long duration. The clinical usefulness of this observation is seriously limited by the lack of correlation just mentioned of this lesion with the other more important and lethal form of vascular disease, i.e., atherosclerosis. Demonstrable calcification of the arteries in young diabetics does seem to correlate with such findings as retinopathy and nephropathy.[6-8] However, it seems to bear no relation to levels of serum lipid in such patients.[9-11] The increased incidence of these calcific deposits, especially in young diabetics, is nonetheless of great theoretical interest. Perhaps an alteration of the ground substance of the connective tissue resulting from the diabetic state may predispose to calcification (see later). It should be mentioned also that at least one group of investigators has maintained that the formation of atheromatous plaques in the intima is always preceded by calcification of the media ("elastocalcinosis").[12-14]

Diffuse Intimal Fibrosis (Hyperplastic Arteriosclerosis).—It has been recognized for many years that there is a fairly uniform and diffuse increase, from birth to old age, of the subendothelial connective tissue of arteries, often associated with splitting of the elastic membranes [15,16] (Fig. 1). This occurs in both diabetics and nondiabetics. The general tendency has been to regard this process as a normal or physiologic accompaniment of aging and as essentially unrelated to the highly lethal and more localized form of arterial disease, atherosclerosis. Recently, however, it has been pointed out that this form of thickening of the intima of arteries is not by any means uniform in all arteries of the body, in all individuals, or in both sexes. For instance, Wilens,[17] in a study of 626 aortas, pointed out that diffuse intimal thickening is more pronounced in arteries that commonly develop atherosclerosis than in those that are infrequently involved,

that it is more pronounced in men than in women, and that it is increased in the presence of hypertension (the latter association has been, of course, well recognized for the smaller arteries). He found that the process was present to a more marked degree in portions of the aorta that commonly develop atherosclerotic plaques. Wilens also observed that species of animals that do not develop spontaneous atherosclerosis also do not show diffuse intimal thickening. He therefore suggested "that the diffuse overgrowth of intimal tissue that occurs consistently early in life is not a natural developmental phenomenon but is related to the same mechanism that eventually leads to the formation of atherosclerotic plaques," also that "atherosclerosis is not a process that is limited to scattered areas of the arterial intima but is one that involves the entire intima."

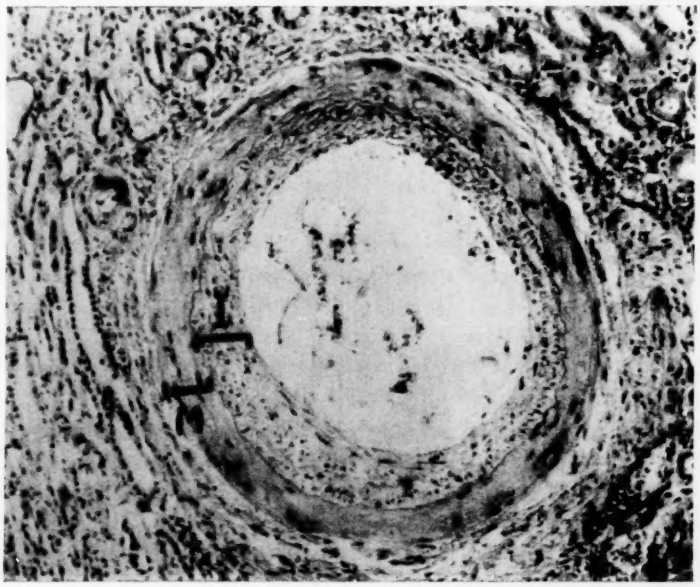

Fig. 1.—Diffuse intimal fibrosis ("hyperplastic arteriosclerosis") in branch of renal artery, diabetic patient. *M* = media. *I* = intima. Hematoxylin and eosin.

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This concept, if true, would suggest that persons who, because of inheritance, maleness,[18,19] hypertension,[20] or other factors, develop a greater than average diffuse intimal thickening might also be expected, for this reason, to have a higher incidence of atherosclerosis. There is not enough evidence to provide any sort of valid answer to this question, particularly as regards diabetes. In fact, in Wilens' own series, of thirty-one diabetic patients, only eleven had intimal thickening greater than that of the mean for their respective age and sex groups. Obviously, the problem merits further investigation.

Taylor[21] has carried the study of diffuse intimal fibrosis a step further by showing that this supposedly "normal" process is often associated with fragmentation of the elastica of the inner media and the deposition of large amounts of metachromatic mucopolysaccharide. He holds that such deposits may play a part in the development of either atheroma or "hyalinization" of the aorta. It

has been suggested elsewhere that the mucopolysaccharides may play a major role in the pathogenesis of vascular disease in diabetes,[22-25] and this point will be returned to later in the discussion.

Another author who has recently emphasized the importance of diffuse intimal thickening, or, as he prefers to call it, "hyperplastic arteriosclerosis," is Moschcowitz.[20] He pointed out that it is impossible to decide where "normal aging" ends and disease begins, and that atherosclerosis is to be regarded as a resultant of various factors, including, in addition to changes in the plasma lipids, alterations in the ground substance of the arterial wall, the intravascular pressure, and "the dynamic effect of time."

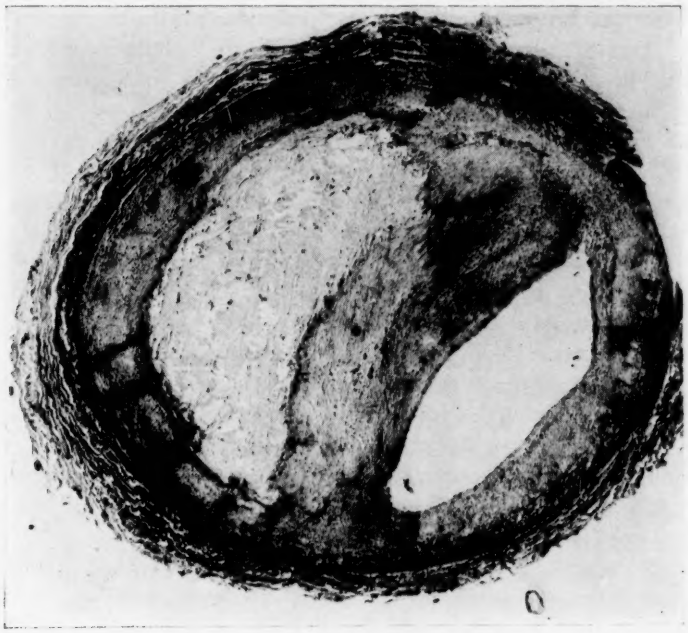

Fig. 2.—Severe atherosclerosis of coronary artery, 34-year-old diabetic woman, with extreme narrowing of lumen. Pale area with empty clefts is the lipid-rich, necrotic zone characteristic of the atherosclerotic process. Hematoxylin and eosin.

Atherosclerosis.—This is the name given to the focal, lipid-containing type of arterial lesion, civilized man's greatest killer (Fig. 2). Since the term is often misunderstood or used in various ways, the definition given by Duff and McMillan[26] is worth quoting: "Atherosclerosis denotes a pathologic change affecting the intima of arteries that is characterized by focal thickenings of the intima in which stainable lipids can readily be demonstrated in and between the cellular elements. The larger lesions show, at the one extreme, an almost exclusively fibrous composition with only minimal quantities of lipid material while, at the other extreme, they contain lipid accumulations of massive proportions with extensive necrosis of the central parts of the lesions commonly culminating in disruption of the intimal lining. The characteristic lesions are highly variable and may present all gradations between these two extremes. Lesions of any composition may show more or less extensive calcification. The term 'atheroma' refers to an atherosclerotic lesion of which the centre is necrotic and occupied by a grumous mixture of lipid material and tissue debris."

1. *Atherosclerosis in general:* No attempt will be made here to review the enormous literature on the subject of atherosclerosis. For discussion and bibliography there are several reviews[3,4,26-35] which may be consulted. The various articles in the Seminars on Arteriosclerosis in the *American Journal of Medicine* in 1951[26,29-33] and the monograph of Katz and Stamler[34] are especially recommended. One of the most thoughtful and provocative of recent reviews is that of Page.[35]

Historically, certain recent trends are discernible. For many years the imbibition theory of Virchow* and Aschoff[38] held sway, followed by various hypotheses, some of which related the intimal lesions to local weakening of the media,[39] to elastic tissue,[15] and to aging of colloids.[40] This gave way to what may be called the cholesterol era, initiated just after the beginning of the present century by the experimental stuffing of rabbits with cholesterol,[41-43] with later extension to other species, especially the chick.[34] This era may be said to have culminated in the hypothesis of Leary[42,43] that atherosclerosis is essentially a disease of cholesterol metabolism and that the intimal plaques begin by the invasion of the endothelium by cholesterol-laden phagocytes. The next, and present, phase may be called the lipoprotein era, initiated by various observations on "macromolecules"[4] and "chylomicrons"[44] and culminating in the work of Gofman and associates,[30,45] who have distinguished various lipoprotein fractions on the basis of their flotation in the ultracentrifuge. Some idea of the current dominance of concepts relating to lipid metabolism, and especially the physicochemical characteristics of the plasma lipids, in research on this disease can be obtained from the proceedings of the American Society for the Study of Arteriosclerosis.[46] This extraordinary preoccupation caused Duff and McMillan[26] to remark: "So popular has this view become that the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the substrate of the vessel wall that it may occur in the absence of the blood vessels themselves."

Recently there have been some signs of a more skeptical attitude toward this great emphasis on lipid metabolism.[46a] It has been shown that the "normal" serum cholesterol varies widely and has little relation (within reasonable limits) to the amount of cholesterol ingested,[47-53] and also that there is no convincing relation between serum cholesterol levels and the cholesterol content of the aorta.[54] Although some persons who have suffered an attack of coronary occlusion have an elevation of the serum cholesterol or lipoproteins of the Sf 12-20 class, there are many who do not (cf. Ricketts[53]). The ratio of cholesterol to lipid phosphorus may be significant,[50] but this also is open to question.

The whole problem of clinical studies of the relation of blood lipids to atherosclerosis is beset by certain fundamental difficulties, some of which are referred to in recent papers.[29,35,54a,54b] The first is that *there are no means of making a clinical diagnosis of atherosclerosis* in the absence of overt manifestations of the disease. In the many studies of young diabetics, for instance, there is no method whatever of ascertaining the presence or absence, size, number, or distribution of atheromatous plaques. It does not, of course, follow that an individual is "free" from vascular disease if he has no clinical signs.[54c]

*This is the view set forth by Virchow in 1856,[36] not the considerably different one in his *Cellularpathologie*.[37]

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A second difficulty, more or less a corollary of the first, and a result of the nigh universal incidence of atherosclerosis in man,[55] is that *there are no normal controls.* In some studies this point has not been given much consideration. As Page[35] said, almost any convenient person willing to give blood has served as a control in some instances. The frequency with which an individual, young or old, in apparently excellent health, unexpectedly suffers a coronary occlusion indicates the extreme hazards of drawing conclusions from such studies. Even the most carefully planned investigations, in which "matched" controls are used,[56] must necessarily suffer from this intrinsic defect.

A third, and most important, difficulty is that *association of two events in time and space does not necessarily imply cause and effect.* This point is too obvious to need elaboration. It applies, of course, not only to all attempts to correlate levels of blood lipids with atherosclerosis, but particularly to comparisons of various racial groups in relation to their dietary intake of fat and cholesterol and incidence of atherosclerosis,[46a,48,52,57,58] where many other factors may be operative. Incidentally, it is interesting that studies on Eskimos are inconclusive.[34] More convincing, perhaps, are studies of familial hypercholesterolemia and coronary disease,[32,49,59] but even here the association could be coincidental.

A fourth difficulty, which applies especially to the experimental study of atherosclerosis in animals as well as to its study in man, is that *there are no means of identifying the earliest lesion.* Since static morphologic methods are being applied to the study of a dynamic biologic process, the results of which can be observed only by killing the animal, or examining the patient post mortem, it becomes purely an assumption when some criterion is applied, such as size of the lesion or lipid content, in judging its age. Thus the earliest lesion of atherosclerosis is, to one observer, a group of lipid-filled phagocytes in the intima,[42,43] to another, fine lipid granules in the same situation,[41] and, to a third,[60] swelling of the ground substance with proliferation of fibroblasts and splitting of the elastic membrane.

There seems no reasonable doubt that disorders of lipid metabolism play a part in the pathogenesis of at least some cases of atherosclerosis. Even if they do, however, no light is thrown on the reasons for the appearance of an atheromatous plaque in a particular spot in a particular artery. Perhaps as a result of this consideration there have been signs of a growing interest in local factors in the arterial wall which may "weaken" it or predispose it to the deposits of lipid which are so characteristic of the disease. Among such studies have been several which have shown the importance of the vasa vasorum in the various incidents and accidents which may occur in the life history of the atheromatous plaque, particularly intimal hemorrhages and thrombosis.[61-65] The thesis that mural thrombi play a major part in the pathogenesis of atheroma, and actually form the substrate for the later development of the lipid-rich plaque, was set forth by Duguid[66,67] on the basis of serial sections of arteries. Geiringer[64] and McLetchie[65] have attempted to combine two of these contributions, holding that the intima must acquire a blood supply when it grows beyond a certain critical thickness, that this adventitious blood supply is liable to interference, and that most of the clinical effects of atherosclerosis can be traced to the resulting ischemic necrosis of the intima.

Interesting attempts have been made recently[68-70] to correlate the localization of plaques with physical factors such as hydrostatic pressure, tissue pressure, structural weaknesses of the vessel wall, and the like, even leading to the interpretation of arteriosclerosis as an "adaptive response," a point of view not far from that of Thoma.[39] One type of local damage, i.e., active inflammation, often not considered in this connection, is emphasized by Saphir and Gore.[71]

Another recent tendency in investigations on arteriosclerosis has been the attempt to produce local lesions of the arterial wall, by trauma, burning,[72] freezing,[73] chemical toxins,[74] etc., in the expectation that lipids will then be deposited in the damaged area. This is an extension of the early work of Anitschkow,[41] who showed that cholesterol could be deposited in injured tissues.

Perhaps the most recent trend in investigation of local factors in the arterial wall has been toward a study of the ground substance, that mysterious gel which fills in the interstices between connective tissue fibers and forms basement membranes.[75-79] In a sense this trend represents a return to the early "imbibition" theory of Virchow, as elaborated by Aschoff,[38] i.e., the concept that the earliest change is a loosening of the ground substance of the intima which then becomes receptive to the deposit of lipids. Newer histochemical methods have facilitated the study of the ground substance, in the arterial wall[80] as well as elsewhere, and it has become clear that it is largely composed of mucopolysaccharides.[81,81a] In fact, a local increase in mucopolysaccharides, presumably deposited from the blood stream, may well be the earliest lesion, preceding any demonstrable deposit of lipid.[60] Here again, of course, one runs into the fundamental difficulty, cited previously, of trying to determine, by morphologic means, the earliest manifestation of a dynamic process.

2. *Atherosclerosis in diabetes:* The fact that diabetics usually develop atherosclerosis at an earlier age and in more severe form than nondiabetics has been amply documented,[8,23,82-86] and no attempt will be made here to review all of the evidence. Among the most impressive of the recent papers on this subject are those of Liebow and Hellerstein,[87,87a] who collected and tabulated data showing a high incidence of coronary sclerosis in diabetes, and Clawson and Bell,[88] who, in a large autopsy series, found fatal coronary disease twice as frequent in diabetic males as in nondiabetic males and three times as frequent in diabetic females as in nondiabetic females. Most impressive of all is the large series (1,559 autopsies) of Bell,[89] who found that about 54 per cent of diabetics over 50 had died of vascular lesions. He noted, incidentally, that since about 30 per cent of older nondiabetics may be expected to die of vascular disease, only about 24 per cent, not 54 per cent, of the deaths of older diabetics in his series should be attributed to the diabetic state. He emphasized also the importance of duration of diabetes, the incidence being extraordinarily high in those whose diabetes began before age 40 and especially in those who had had the disease for twenty years or longer. Similar conclusions have, of course, been reached by many of the other observers cited here.

Although emphasis is usually placed on coronary disease because of its lethal aspects, the association of diabetes and vascular disease is striking in other parts of the body as well.[90-95] In clinically manifest vascular disease of the extremities,

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Wessler[96,97] has discovered abnormal glucose tolerance tests so frequently that he recommends such tests in all patients with peripheral vascular disease, finding that the presence of this aberration has prognostic as well as diagnostic value.[98]

It is quite possible that disturbed lipid metabolism is the basis for the high incidence of atherosclerosis in diabetes and that treatment should be directed along this line, by dietary or other means.[99,100] However, difficulties arise in attempting to explain the higher incidence of atherosclerosis in diabetics on the basis of levels of serum lipids. Man and Peters[101] found that a majority of a series of diabetics without complications such as dehydration, acidosis, cirrhosis, or renal disease had serum cholesterol levels within accepted normal limits. Ricketts[53] called attention to the remarkable paucity of studies of serum lipids extending over a period of years in treated diabetics. Chaikoff and associates[102] found no appreciable difference between a group of normal children and a group of diabetic children under good control with respect to serum cholesterol, phospholipids, and fatty acids. In 273 adult diabetics, Pomeranze and Kunkel[103] found elevated serum lipids in only about one-half. As regards lipoproteins, Barach and Lowy[10] found elevations (over 50 mg. per 100 c.c.) of the Sf 12-20 group in less than one-half of their series. Of particular interest are the findings of Hanig and Lauffer,[104] who found no clear difference in Sf 12-20 levels between groups of "normal" males and diabetic males with or without demonstrable cardiovascular disease, *when both high and low values were given equal weight* in analyzing the data. No definite difference between diabetics and nondiabetics is apparent in the study of Keiding and co-workers,[9] although there did appear to be a higher lipoprotein level in poorly controlled diabetics. Collens and co-workers[54a] found in a series of diabetics with atherosclerosis but without clinical nephropathy that the lipoproteins fell largely into categories often accepted as normal. It is noteworthy that, in all these studies, there is a large number of diabetics whose serum lipids are well within normal limits. It is conceivable, of course, that repeated episodes of coma and acidosis might be of great importance.[11,105] On the whole, as Ricketts[53] so succinctly pointed out, there is by no means any clear or substantial evidence that the increased incidence of atherosclerosis in diabetes is attributable to an elevation of any of the serum lipids or to a disturbance in lipid metabolism. Valuable information should be forthcoming soon in the report of the Study of Lipoprotein and Atherosclerosis sponsored by the National Heart Institute. Whether the metabolism of lipotropic substances is involved is uncertain.[106-108]

At this point it should be emphasized that in the experimental animal there is no convincing evidence that diabetes predisposes to atherosclerosis. In fact, alloxan diabetes has been shown to inhibit the development of experimental cholesterol atherosclerosis in the rabbit.[109,110]

The concept of the role of the ground substance and mucopolysaccharides (cited previously) naturally leads to the question of a possible disturbance in the metabolism of these substances in diabetics as an explanation of susceptibility to atherosclerosis. The problem of mucopolysaccharides will be discussed more fully later in relation to the lesions of smaller vessels; suffice it to say here that it is possible to conceive of the increased susceptibility of diabetics to vascular disease as dependent on altered metabolism of these substances which are components of "ground substance" and basement membranes of blood vessels.[22,23]

Studies along these lines are in their infancy, and it remains to be seen whether this working hypothesis has any validity.

It may be remarked in passing that it is a striking fact that diabetes seems to obliterate the usual sex difference in the incidence of coronary occlusion (Fig. 2). Whereas in nondiabetics coronary occlusions occur in males several times as frequently as in females, in diabetics the incidence in the sexes is approximately equal.[23,86,89,111a] The low incidence in nondiabetic females has been attributed to the presence of estrogens.[111,111a] Estrogens apparently have an inhibitory effect on experimental cholesterol atherosclerosis in chicks.[111a,112,113] In fact, efforts have been made to treat males who have had coronary occlusion by the administration of estrogens.[114] A remarkably high incidence of abnormal glucose tolerance curves is seen in diabetic females with clinical evidence of vascular disease of the extremities.[97,98] Is it possible that in diabetic females there is a deficiency of estrogen, or a shift in the balance of estrogens and androgens so that the protective effect of estrogen, whatever it may be, is nullified?

In summary, it appears that the differences in diseases of the larger arteries between diabetics and nondiabetics are quantitative rather than qualitative. The only objective evidence that there might be qualitative differences seems to be that of Lundbaek and Posborg-Peterson,[115] who performed chemical analyses of segments of sclerotic coronary arteries from nondiabetics and from diabetics of long standing. They found a lower calcium content in the diabetics. There was no difference in the total content of cholesterol and phospholipids, but the proportions of the phospholipid constituents were different in the two groups, the cephalin content being higher and the lecithin content "probably" lower in the arteries from diabetic patients than in those from nondiabetic patients. The authors concluded that these differences suggest "a specific lipid composition of the arteries in long-term diabetes." There is considerable scattering in the tabulated results of these authors, and, needless to say, confirmation of such potentially important findings is desirable.

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LESIONS OF THE ARTERIOLES (ARTERIOLOSCLEROSIS)

Ever since the classical paper of Moritz and Oldt,[116] it has been recognized that the common lesions of the smallest arteries or arterioles are:

1. Medial hypertrophy.
2. Intimal fibrosis (hyperplastic arteriolosclerosis).
3. Intimal hyalinization.

These lesions, in varying combinations, are found, particularly in the kidney, in cases of long-standing essential hypertension ("benign nephrosclerosis") but also in association with the hypertension of other diseases, e.g., pyelonephritis, and sometimes in the absence of hypertension.[117-120] The hyperplastic arteriolar lesion, consisting of concentric laminated layers of fibrous tissue in the intima, often with reduplication of the elastic lamellae, is apparently the equivalent of the diffuse intimal fibrosis of large arteries, discussed previously, and is particularly striking in the arterioles of the kidney in cases of accelerated hypertension from any cause. Under these circumstances it may, of course, be seen in diabetics. Moschcowitz,[121] however, holds that it has particular, even etiological, importance in diabetes.

Perhaps the most characteristic, at least the most obvious, lesion of the arterioles in benign nephrosclerosis, and the one likely to be quantitatively increased in diabetes, even in the absence of hypertension, is hyaline intimal thickening or intimal hyalinization. This may be seen in various tissues, but is most prominent in the kidney, where it affects aspecially the preglomerular arterioles and the afferent (and, in diabetes, the efferent) arterioles of the individual glomeruli (Fig. 3). It consists of a homogeneous, hyaline-appearing, acidophilic material, which usually appears to lie between the endothelium and the internal elastic lamella, but occasionally seems to envelop the internal elastic lamella and to replace part of the media.

Fig. 3.—Hyaline thickening of both afferent and efferent glomerular arterioles. PAS stain. Same case as in Fig. 2.

The pathogenesis of this lesion is quite obscure. In fact, it is interesting that two widely different hypotheses regarding it have been advanced in the recent literature. On the one hand, Duguid and Anderson[122] have put forth what appears to be an extension of Duguid's hypothesis of the pathogenesis of atherosclerosis, mentioned previously.[66,67] These authors hold, on the basis of conventional histologic methods, that the hyaline substance is derived from the circulating blood, that it is deposited next to the endothelium, and is eventually covered over by endothelium. They suggest that the substance may be something akin to amyloid or "preamyloid." In support of their concept they reason that a "degenerated" vessel should be dilated, not narrowed.

In contrast, Montgomery and Muirhead,[123,124] pointing to certain histochemical and microspectroscopic similarities between the hyaline of arteriolar sclerosis and the necrotic smooth muscle of the media of arterioles in nephrectomized

dogs, suggested "that the hyaline substance is not deposited from a hematogenous source, but represents the ultimate fusion of products derived from necrotic smooth muscle, and that, therefore, hyaline in arteriolar sclerosis is autochthonous." Clearly, the existence of two such conflicting theories of the pathogenesis of hyaline arteriolosclerosis only serves to emphasize our ignorance.

It has been known for many years that lipids may be found as one of the constituents of the hyaline material in this condition. Wilens and Elster[125] not only found that lipid was a frequent finding in hyaline arterioles, but also concluded that the lipid was quantitatively increased in hypertension and in diabetes with or without hypertension. They emphasized particularly the large amounts of lipid in the arterioles of diabetic females as compared with nondiabetic females or even with diabetic males. Baker and Selikoff,[126] using the Schultz histochemical reaction for cholesterol, concluded that most of the hyaline arterioles they examined contained cholesterol, and that the frequency seemed to be greater in cases of hypertension. (No particular observations on diabetes are recorded.) They felt that the presence of cholesterol indicated a "similarity" of arteriolosclerosis to atherosclerosis. Sommers and co-workers[127] showed that hyaline arterioles in various disease states, including diabetes, have a similar ultraviolet absorption pattern. This is in contrast to their findings in glomeruli[128] (see later).

McManus,[129,130] on the basis of a positive reaction with the periodic acid-Schiff reagent method, referred to the hyaline material in arteriolosclerosis as a glycoprotein. This finding is readily confirmed, and there seems to be little question that carbohydrate of some sort is present in the hyaline material.*

The fact that arteriolosclerosis of the hyaline type is indeed greatly increased in frequency and severity in diabetes is clearly and forcefully brought out in Bell's[134] important study of the kidney in 1,465 autopsies.[134] He concluded that in many cases arteriolosclerosis may be attributed to "the diabetic state," since in his series it was present in over one-half of elderly diabetics *without hypertension* (the absence of hypertension was confirmed by the lack of cardiac hypertrophy in this group). A striking, and perhaps specific, feature of arteriolosclerosis in the diabetic is that the efferent arteriole of the glomerulus often shows severe involvement in addition to the afferent one. No explanation is at hand for this interesting finding. Bell also pointed out that the hyalinized afferent arteriole is usually thicker than it is in essential hypertension without diabetes and that this in itself is highly suggestive of diabetes. He also found an increased severity of the lesion with increasing duration of diabetes, especially in the younger diabetics, and suggested that the eventual development of hypertension in the diabetic may be due to this lesion. Robbins and Tucker[135] also found a high incidence in diabetes.

Although hyaline arteriolar sclerosis is perhaps most obvious and most important in the kidney of the diabetic patient, it also affects the eye, and may play a significant part in the retinal disabilities which are so distressing in many of the young diabetics (Fig. 4). In fact, Ashton[135a] suggested that narrowing and occlusion of arterioles, with resultant ischemia and formation of new vascular channels, is a major factor in the total picture of diabetic retinopathy.

*It must be noted that the periodic acid-Schiff reagent method, on which far-reaching conclusions have been based, is not absolutely specific for carbohydrates. Some proteins and amino acids give the reaction[131-133] while hyaluronic acid and chondoitin sulfate do not.[133a,133b]

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LESIONS OF THE CAPILLARIES AND VENULES

Disease of the smallest blood vessels in diabetes seems to be practically confined, for reasons unknown, to the kidney and the eye. It will be convenient to consider the lesions in these two organs separately, and then to inquire as to whether there is any fundamental pathogenetic relation between them.

Intercapillary Glomerulosclerosis.—Although the capillary lesions in the kidney are also referred to as "diabetic glomerulosclerosis" and "Kimmelstiel-Wilson lesion," the original term "intercapillary glomerulosclerosis" has become fairly well established by usage.

Fig. 4.—Arteriolosclerosis (right) and phlebosclerosis (left) in retina of 34-year-old diabetic female (same patient as in Fig. 2). Hematoxylin and eosin.

In 1936 Kimmelstiel and Wilson[136] described eight cases in which a peculiar renal lesion was associated with a clinical syndrome of gross albuminuria, edema of nephrotic type, and a history of diabetes. Actually, the clinical features were not clearly delineated in this original report, and, in fact, the diagnosis of diabetes was not established in one of the patients. Since the original description of the clinical and pathologic features of this syndrome, a large volume of literature has accumulated. Since several excellent reviews are available,[137-147] most of them with fairly comprehensive lists of references, no attempt will be made here to survey all of the available literature in minute detail. Instead, emphasis will be placed on certain aspects of the condition which have assumed importance in recent years: (1) the nonspecificity of the clinical syndrome, (2) the specificity of the histologic lesion, (3) the so-called "exudative" lesion, and (4) the probable pathogenesis of the lesion, including attempts at experimental reproduction in animals.

1. *Nonspecificity of the clinical syndrome:* For some years following the original paper, the impression persisted in the literature that the clinical syndrome was reasonably characteristic and correlated well with the presence of the renal lesion. In their review in 1948, Kimmelstiel and Porter[139] appeared to agree with the statement of Henderson and associates[141] that "the presence of the advanced lesion can be predicted with considerable certainty," and reference is often made to "the Kimmelstiel-Wilson syndrome."[148-150] Recently, however, doubts have been expressed as to the accuracy of clinical diagnosis in relation to presence or absence of the anatomic lesion. More emphasis has been placed on "variants" in the clinical picture.[151,152]

Of particular interest is the recent study of Rogers and Robbins.[145] They reviewed the records of 229 diabetics with reference to the classical triad of albuminuria, edema, and hypertension and evaluated them on strictly clinical grounds as to the "possible" or "probable" presence of intercapillary glomerulosclerosis. After correlation of the clinical diagnoses with the autopsy findings, it was found that, of the forty-one patients selected clinically as having the renal lesion, only twenty-eight proved to have it, a false positive error of 32 per cent. Also, there were thirty-eight cases in which the anatomic lesion was present that were not selected clinically; hence, of a possible sixty-six cases, only twenty-eight were correctly identified. In another study Rogers, Robbins, and Jeghers[146] compared 100 diabetics with proved intercapillary glomerulosclerosis with 176 diabetics not having this glomerular lesion. They found that with increasing duration of diabetes there was an increase in the incidence of intercapillary glomerulosclerosis, but no correlation was found with severity of diabetes. Hypertension, albuminuria, azotemia, and cardiac failure were all more frequent and severe in the patients with intercapillary glomerulosclerosis. However, the various features occurred together to produce a clinically recognizable syndrome in only twenty-five of the 100 patients with intercapillary glomerculosclerosis; it also occurred in five of the control group of diabetics. They conclude that "many if not most cases of intercapillary glomerulosclerosis do not present the classic triad of clinical findings; moreover, the classic pattern may occasionally be found in diabetic patients not having intercapillary glomerulosclerosis."

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It is possible that the accuracy of clinical diagnosis may be increased by the use of other criteria, such as the presence or absence of doubly refractile lipids in the urinary sediment,[140,144,152] which is, however, also nonspecific and subject to considerable difficulties of a technical as well as interpretive nature.[153] Perhaps of some value also may be the unexplained absence of ketosis often (but not always) observed in these patients, and the remarkable fact that with onset of the intercapillary lesion, glycosuria often diminishes.[154,155] The latter finding is also unexplained unless it be due to the diminished glomerular filtration often found in these patients.[156] The lessened hyperglycemia and lowered response to insulin that may also be encountered is not so readily explained.[152,155] However, a recent study[156a] indicates that such changes are inconstant, that they are more closely related to the clinical syndrome than to the renal lesion (which may be absent) and that decreased intake of food may contribute greatly to the amelioration of the diabetes, when it occurs.

2. *Morphology and specificity of the glomerular lesion:* It is necessary to define the lesion in morphologic terms before considering its specificity, since confusion has arisen from failure to do this in the past. Considerable clarification of the field occurred when Bell[157] delineated a *nodular* and a *diffuse* form of the disease. This is of great importance, since the nodular type is the one which is characteristic of, and indeed, probably specific for, diabetes. It appears to be the same as that designated as "severe degree' by the original authors.

The *nodular* lesion occurs typically as a spherical or ball-like, hyaline, acidophilic mass, situated toward the periphery of the glomerular tuft, often with an

apparently intact capillary running over its surface (Fig. 5). This capillary is patent and often dilated. The hyaline mass often contains nuclei but these are usually distributed around its periphery. Often the hyaline material appears laminated[137,142] (Fig. 6). A similar lesion may appear in chronic glomerulonephritis, but in this case each tuft of the glomerulus is usually involved uniformly, giving a lobulated appearance ("lobular glomerulonephritis"), the peripheral capillary is not so distinct, and the afferent arteriole is usually not hyalinized [134,137,142] (Fig. 7).

Fig. 5.—Glomerulus from diabetic kidney, showing at right two ball-like hyaline masses with enveloping capillaries, also diffuse "axial thickening." Periodic acid, Schiff reagent.

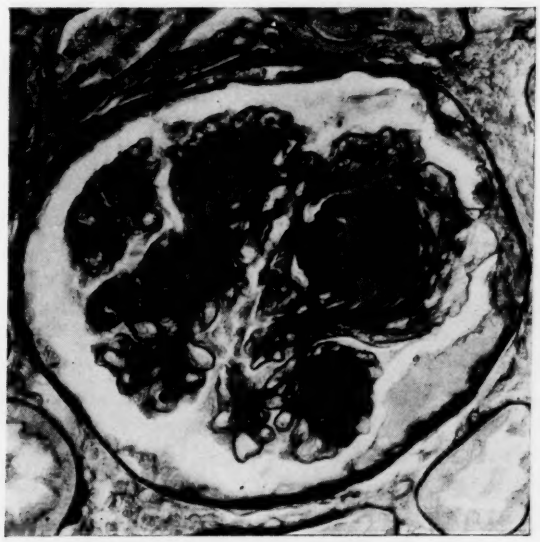

Fig. 6.—Large nodule of intercapillary glomerulosclerosis with lamination. Periodic acid, Schiff reagent.

The hyaline substance making up the nodular lesion is acidophilic, often laminated, argyrophilic, and more resistant to tryptic digestion than are capillary walls in general.[137,142] It reacts with the periodic acid-Schiff reagent method,[129,130] often contains fat,[158] and has fairly distinctive characteristics with phase microscopy and ultraviolet absorption[128] (see further discussion later).

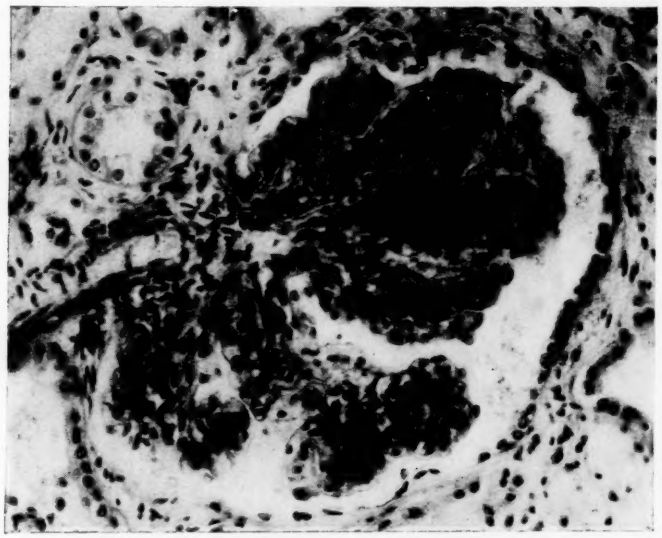

Fig. 7.—"Lobular glomerulonephritis," nondiabetic, showing more uniform thickening of glomerular tuft, and lack of hyalinization of afferent arteriole. Hematoxylin and eosin.

One of the unresolved questions in the study of the classical nodular lesion is whether it is situated between the capillaries of the glomerular tuft or in their walls, i.e., whether it is intercapillary or intramural. Most writers seem to have gone along with the original authors[136] in embracing the former concept, but a few others, notably Allen[137,142] and Bell,[134] have maintained the latter point of view. This difference of opinion seems to be based chiefly on whether or not one accepts the presence of a "mesangium" or intercapillary connective tissue extending out to the periphery of the glomerular tuft. Recent work[159-161] seems to support an older concept[162-164] that there is at least a potential "intercapillary" space between the basement membranes of the endothelium and epithelium, which normally appear as a single membrane. Rinehart and co-workers,[165] using special staining methods devised by them, claim to distinguish epithelial and endothelial elements and refer to the nodule of diabetic glomerulosclerosis as "a swelling or excess deposition of the endothelial cytoplasm." Doubts have recently been expressed concerning the supposed duality of the basement membrane.[166] Any theory of histogenesis must, as Berkman[25] pointed out, explain the almost constant sparing of the capillary wall on the *outside* of the hyaline mass, which certainly suggests an "axial" origin. Perhaps, as Rifkin and co-workers[144] suggested, the question cannot be resolved with present methods. At any rate, as has been pointed out, the phrase "intercapillary glomerulosclerosis" can stil

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serve by usage as a descriptive term,[139] even though it is nonspecific when interpreted literally.[147]

Fahr[167] appears to have a special interpretation. He makes an analogy between the structure of the glomerular tuft and the renal tubule and considers the lesion as "extracapillary glomerulosclerosis."

The *diffuse* lesion of intercapillary glomerulosclerosis was apparently described first by Spühler and Zollinger[168] as "diffuse hyalinization of the mesangium" and in the following year by Laipply and associates.[138] The minimal lesions which the latter authors included have not been accepted by most other investigators. In fact, no clear description of this lesion appears to be available. Bell[134] seems confident that it is an entity. Although he did not describe it in any detail, his illustrations show a diffuse thickening of the "intercapillary septa." He apparently feels that this lesion is more common than the nodular form, and that it may either progress into the nodular form or continue on without nodule formation until the glomerulus is finally destroyed. Bell seems to believe that the diffuse lesion is readily recognized, provided that chronic glomerulonephritis can be excluded (this being done chiefly on the basis of lack of arteriolar hyalinization in the latter disease). He also said that "intercapillary lesions do not develop in primary hypertension," and that "when chronic glomerulonephritis has been excluded, diffuse intercapillary sclerosis is highly specific for diabetes."

It is probably safe to say that most students of the subject do not share Bell's confidence in distinguishing the diffuse lesion in diabetes from similar "axial thickenings" in such diseases as benign nephrosclerosis and pyelonephritis.[23,142,168,169] Robbins and co-workers[147] indicate that nephrosclerosis may cause axial thickening in a glomerulus which also contains the nodular lesion. The general confusion is indicated by Anderson,[170] who found *no* instances of the diffuse lesion in ninety-two diabetic kidneys. Perhaps the kidney biopsy technique[171] will help to answer the question of whether the diffuse lesion may be a precursor of the nodular, as well as helping to determine whether other complicating diseases, especially pyelonephritis, may be present, as so often happens in "diabetic nephropathy."[172]

It is undoubtedly true that hyaline thickening of the glomerular arterioles is a helpful sign, and that hyaline change in the *efferent* arteriole is so characteristic of diabetes as to be almost specific[134] (Fig. 3). Occasionally, however, intercapillary glomerulosclerosis may occur with minimal arteriolar change.[147] The involvement of the efferent arteriole, when it does occur, suggests that changes in renal hemodynamics might be revealed by function tests. A decreased renal plasma flow, decreased glomerular filtration rate, and decreased maximum tubular resorption of glucose have been described,[144,156] and one observer reports a decreased filtration fraction.[173] A "unique" increase in ratio of renal oxygen consumption to renal tubular mass is said to occur in diabetic nephropathy.[174]

Finally, as to specificity, it seems probable that the typical, full-blown, nodular lesion is almost, if not absolutely, pathognomonic of diabetes mellitus.[23,134,142,144,147] Indeed, in those cases in which it has been reported in nondiabetics, one may question (a) the adequacy of the clinical history and examination, and (b) the scrupulousness of the histologic criteria which were applied.

In this connection the fact that anatomically typical cases occurring in alleged nondiabetics have proved, on careful investigation, to have a history of diabetes[147] is worth emphasizing. The remarkable fact that glycosuria may diminish or disappear with the onset of the Kimmelstiel-Wilson lesion[154,155] may account for some missed cases of diabetes. As regards the *diffuse* lesion, claims for specificity[134,138,175] do not seem to be generally supported.

It may be remarked at this point that it is quite natural that confusion should have arisen with regard to this lesion, inasmuch as it is now recognized that the kidney of the long-duration diabetic may show at least three diseases: arteriolosclerosis, intercapillary glomerulosclerosis, and pyelonephritis—a situation sometimes covered by the term "diabetic nephropathy."[172]

3. *The "exudative" lesion:* In speaking of intercapillary glomerulosclerosis, most authors (see previous references) have either referred to the nodular and the diffuse lesions as distinguished by Bell, or else have ignored the diffuse lesion altogether. Recently, and especially in the last two years, there has been apparent an increasing emphasis on what some writers regard as a third type of lesion in intercapillary glomerulosclerosis, called the "exudative" type by British workers.[95,170]

It is usually stated that these changes were first described by Fahr.[167] However, this is incorrect. They were described and illustrated by Kimmelstiel and Wilson[136] in their original communication. Apparently little importance was attached by them to these findings. In 1939 Hückel[176] illustrated "hyaline-fibrinoid" masses, partly in the capsule. In 1940 Simon[177] described "lipohyalin" in the capsular space. Allen[137] in 1941 mentioned "crescentic deposits of sudanophilic material" in Bowman's space and concluded, as did Kimmelstiel and Wilson, that they had no differential significance. Subsequently Fahr[167] described similar lesions. Then Spühler and Zollinger[168] described and illustrated "fibrinoid caps" and capsular masses which stained red with the trichrome stain which they used. The greatest popularity of these lesions has, however, been achieved in the last two years. Koss,[178] studying "severely damaged" kidneys of diabetics, described what he called "hyaline-fibrinoid" material in the glomeruli. This appeared in hematoxylin-eosin slides as a "highly eosinophilic, glossy material with a faint bluish hue," in the form of acellular crescents or round or oval masses, sometimes containing vacuoles, and situated at the periphery of the glomerular tuft. Koss encountered the same difficulty that subsequent authors have found in trying to localize the material in relation to the structural elements of the glomerulus. He pointed out that it was often covered by the visceral layer of Bowman's capsule, and hence did not usually lie with the capsular space, but as to whether its location in the tuft was intracapillary or intercapillary he was often uncertain. Koss showed that in general the material had the staining characteristics of fibrinoid as set forth by Altshuler and Angevine,[179] that it often contained stainable fat, and that it showed many tinctorial differences from the nodular lesions of intercapillary glomerulosclerosis, as well as having a more homogeneous, hyaline, glossy appearance. He noted also that it might appear in the wall of Bowman's capsule and occasionally in the basement membrane of a convoluted tubule, also frequently in the arterioles. From the clinical point of

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view, he found that several patients had had a drop in their insulin requirements and that acidosis was rare (similar findings have been noted by others[154,155] in diabetics with severe renal damage). Several patients had also experienced a rapid downhill course to uremia.

In a control series of cases of nephrosclerosis, Koss found hyaline-fibrinoid material in the arterioles (less marked than in the diabetics) and only rarely in the glomeruli. He concluded that its specificity for diabetes was quantitative rather than qualitative. As regards the nature of the substance, he considered that it was in all probability a precipitated protein accumulating between the two layers of the basement membrane of the glomerular capillaries, and "in every way comparable to arteriolar hyaline sclerosis."

Barrie and co-workers[180] observed, in sixteen of 290 necropsies on diabetics, a "crescent of material staining like fibrin . . . between the basement membrane and the endothelium of the renal glomerular tufts." This they called the "fibrin cap" and concluded that it occurred half as commonly as intercapillary glomerulosclerosis but that it had the same age incidence and relation to hypertension. They considered that it could occur independently of intercapillary glomerulosclerosis but that it was always associated with severe arteriolosclerosis. Similar material in Bowman's capsule they called the "capsular drop" (cf. Fig. 10).

Randerath[181] has illustrated similar lesions. Hall[95] and Anderson[170] have dubbed them "exudative lesions" and have not, apparently, considered them of great importance. Anderson[170] stated, "The exudative lesion seems to differ from the nodular in degree rather than in kind, and, since no attempt at repair is ever seen, the exudative lesion is probably a terminal event."

Bloodworth and Hamwi,[182] in connection with attempts to reproduce the lesions experimentally (see later), studied the staining properties of the human lesion and came to essentially the same conclusions as Koss,[178] i.e., the reactions of the exudative lesion are more like those of fibrin or fibrinoid than are those of the nodular lesion.

The so-called exudative lesion can be found without difficulty in some advanced cases of intercapillary glomerulosclerosis (Figs. 8, 9, 10). It also appears occasionally in other conditions, e.g., chronic glomerulonephritis (Fig. 11), and one wonders whether it may not be an occasional nonspecific accompaniment of the nephrotic syndrome, perhaps representing an accumulation, in the capillary lumen or wall or in the capsular space or wall, of lipoprotein-mucopolysaccharide complexes filtered by the diseased glomerulus.

4. *Attempts at experimental reproduction of intercapillary glomerulosclerosis:* It is probably fair to state that a convincing replica of the generally accepted nodular lesion of Kimmelstiel and Wilson has not been achieved in experimental animals. Whether "diffuse" or "exudative" lesions have been reproduced is uncertain, but also open to question.

It has been customary to state that Lukens and Dohan[183] encountered a good example of intercapillary glomerulosclerosis in a dog which had been made diabetic with anterior pituitary extract and maintained in the diabetic state for five years. However, a re-examination of their illustration does not lead to the conclusion that they found the typical, ball-like, hyaline nodule with peripheral patent capillary.

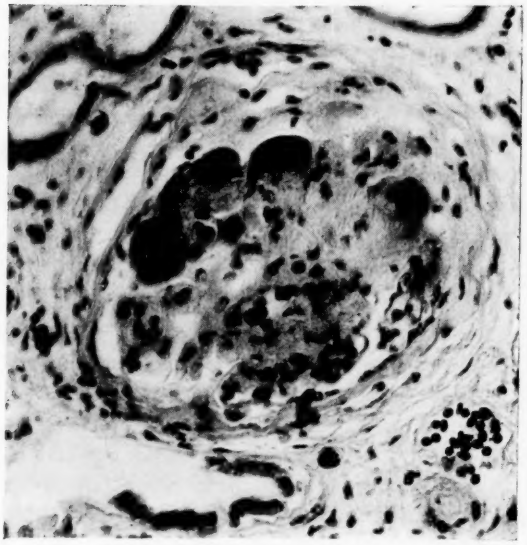

Fig. 8.—"Exudative lesion" in glomerulus of diabetic kidney showing intercapillary glomerulosclerosis. The dark, hyaline, droplike masses are bright red in original slide. Eosin-methylene blue.

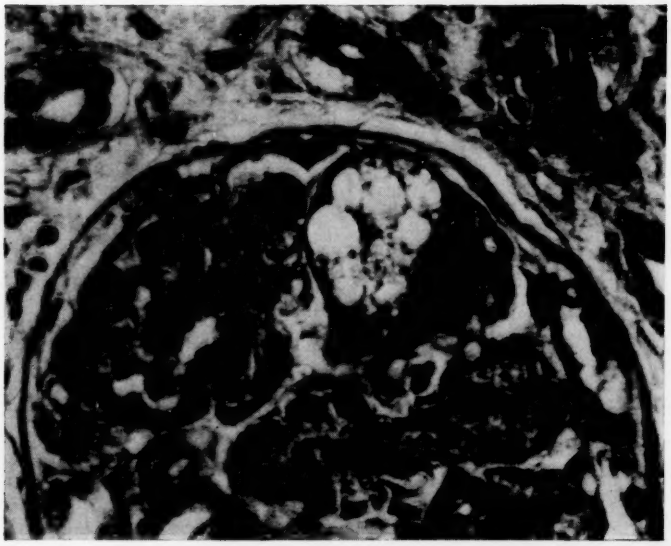

Fig. 9.—Another example of the "exudative lesion" in diabetic kidney. Hyaline masses in glomerulus, not clearly intra- or intercapillary in location. One is quite vacuolated. Hematoxylin and eosin.

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Fig. 10.—Fat stain of "exudative lesion" in diabetic kidney. Dark masses red in original. "Capsular drop" at right. Frozen section. Oil Red O.

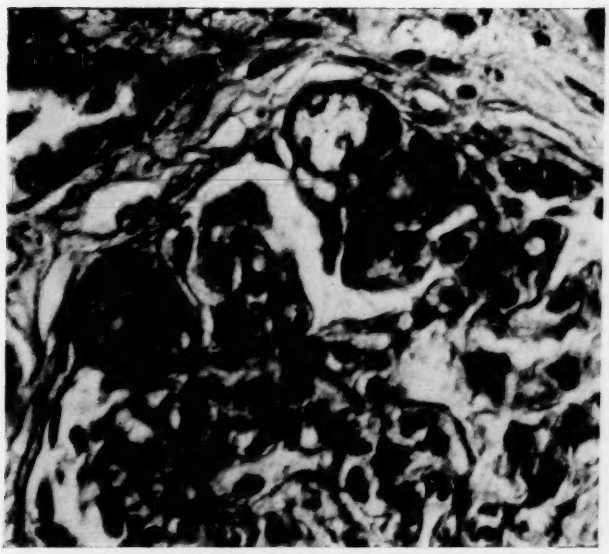

Fig. 11.—"Exudative lesion" in nondiabetic kidney. Hyaline, vacuolated masses in glomerulus of case of chronic glomerulonephritis with nephrotic syndrome.

Mann and Goddard[184] described a lesion in alloxan diabetic rats consisting of a thickening of the basement membrane of the glomerular tuft, followed by deposition of hyaline, acellular material between the capillary loops. In contrast to the human lesion, there was considerable proliferation of reticulin fibers, adhesions were found from one tuft to another or from tuft to capsule, and there was proliferative activity on the part of both endothelial and epithelial cells.

A similar, perhaps the same, lesion was described by Foglia and co-workers[185] in rats made diabetic by partial pancreatectomy. In both this paper and the one just mentioned, considerable stress is laid upon multiplication of reticulin fibers in the glomeruli. It is not clear that this is an essential feature of the human "diffuse" lesion, i.e., the one to which these experimental lesions bear some resemblance. On the other hand, no really clear and minute description of the diffuse lesion in man seems to be available, even in the writings of those who place most emphasis upon it.[134,138]

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Recently great interest was stimulated by the report of Rich and co-workers[186] of aneurysmal dilatations of glomerular capillaries and nodular structures resembling the Kimmelstiel-Wilson lesion in rabbits given large amounts of cortisone in the course of a study on experimental glomerulonephritis. No claim has been made that the lesions constitute an exact reproduction of the classical nodular lesion of Kimmelstiel and Wilson.[187] These lesions appear to me* to consist essentially of hyaline, acidophilic, sometimes vacuolated deposits which seem in most instances to lie within the lumen of a dilated capillary loop (Fig. 12). Admittedly, as in the case of the human exudative lesion described previously, it is often difficult or impossible to determine whether the deposit is in the lumen of a capillary, between capillaries, or in the capsular space (Fig. 13). However, the occasional appearance of red blood cells within the hyaline material (see also Fig. 14) strongly suggests that, at least in some cases, the hyaline material represents an intravascular coagulum of constituents of the blood plasma.

Subsequently Becker[188] mentioned what appear to be identical lesions in rabbits made diabetic with alloxan and given cortisone. Some of these rabbits also had capillary microaneurysms in the retina, and Becker laid considerable stress on a possible role of the adrenal cortex in the production of both the renal and retinal lesions. Subsequently Becker and co-workers[189] found that omission of supplementary viatmin B-12 and Aureomycin from the diet of the animals would "potentiate" the renal lesions induced by cortisone, and that heparin would suppress them.[190]

The most careful and extensive study to date of this type of experimental renal lesion is that of Bloodworth and Hamwi.[182] They gave rabbits 5 or 10 mg. of cortisone daily intramuscularly for a minimum period of twenty-one days. Lesions appeared concurrently with albuminuria in the animals and were sometimes seen as early as thirteen days. Maximum frequency of the lesions was found between twenty-one and forty days. After this time, even though cortisone was continued, the lesions gradually decreased in number. In general they found lesions in 5 to 10 per cent of glomeruli. Special stains and serial sections

*In slides kindly furnished by Dr. Rich.

were interpreted as indicating that the lesions were predominantly within the lumen of dilated capillaries. In some cases trapped red cells were seen within the eosinophilic mass, as shown in Fig. 14, which is reproduced with their kind permission from one of their slides. They also described an occasional crescentic mass of eosinophilic material in Bowman's space and sometimes eosinophilic material in the intercapillary space adjacent to one of the experimental lesions.

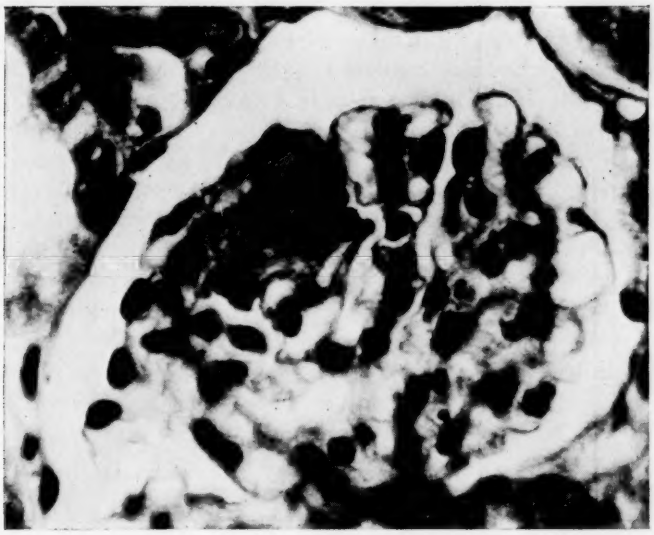

Fig. 12.—Experimental lesion in kidney of rabbit given cortisone. There is a faintly vacuolated hyaline mass, possibly intracapillary. From slide kindly loaned by Dr. Arnold Rich. Hematoxylin and eosin.

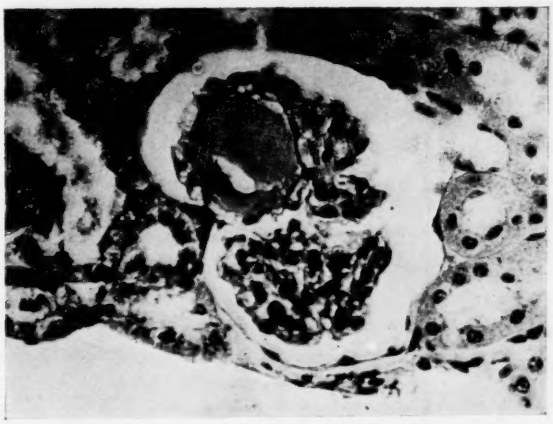

Fig. 13.—Experimental lesion in rabbit given cortisone. Here a capillary appears to pass over the hyaline mass. Photograph by courtesy of Dr. Arnold Rich.

They described about one-half of the experimental lesions as sudanophilic and stated that they are Schiff-positive after periodic acid, although less intensely so than similar human lesions. In animals treated for a longer period (four months) they found arteriolar sclerosis, focal pyelonephritis, and a diffuse thickening of the intercapillary septa which they interpreted as similar to the "diffuse" lesion in man. They also mentioned occasional glomeruli as showing nodular masses "quite closely resembling the nodular lesions of human diabetic glomerulosclerosis." However, they do not seem to have illustrated this form of lesion.

Bloodworth and Hamwi summarized their results by suggesting that the experimental lesions resemble most closely the human "exudative" type, and that the eosinophilic intracapillary masses, containing mucopolysaccharide and lipid, may eventually diffuse into the intercapillary space to produce a diffuse thickening. However, they noted that the early lesions in their material tended to disappear and apparently they were not able to demonstrate convincing transitions from one type of lesion to the other.

More recently Wilens and Stumpf[191a] have reported similar observations in rabbits treated with cortisone and have raised the question of whether alteration in blood lipids may be a factor in causing the lipid-rich deposits in the dilated glomerular capillaries.

In unpublished work at the New England Deaconess Hospital[191] similar eosinophilic, periodic acid, Schiff-positive masses were found within glomerular capillaries in rare instances in alloxan diabetic rabbits given cortisone in large doses (Fig. 15). These were not, however, considered as resembling the lesions of the human diabetic kidney.

Of considerable interest in this connection is the work of Sussman and Freed,[192] who reported hyaline masses in the glomeruli of rabbits given large amounts of gamma globulin intraperitoneally and maintained in a state of hyperglobulinemia over a long period of time. Their illustration bears a strong resemblance to the type of intracapillary coagulum just discussed.

5. *Pathogenesis of intercapillary glomerulosclerosis:* This disease has such distinctive features and such a remarkably close association with diabetes that any simple concept that intercapillary glomerulosclerosis is "merely a severe form of arteriolosclerosis with extension into the glomeruli"[193] or "the logical conclusion or end stage of slowly progressive, primary, glomerular arteriosclerosis"[194] would seem to be inadequate.

Hypotheses such as those just quoted are, in fact, apparently negated by modern histochemical and biophysical methods. Allen,[137] in his original paper, showed that the hyaline nodules of this disease differ from other types of hyaline in being more resistant to tryptic digestion. McManus[129] showed that they gave a strong reaction with his periodic acid-Schiff reagent method and that this reaction was removed by digestion with pectinase,[130] suggesting that polysaccharides were an important component. Wilens found a high lipid content in some cases. Churg and Grishman,[159] using phase microscopy, found the hyaline nodules to consist of vacuolated or lamellated material which they localized in the intercapillary space. They concluded that the same spongy material made up the axial thickening of the diffuse form of the disease and that the latter probably precedes the nodular form.

Most important of all, perhaps, are the recent studies of Sommers and co-workers,[128] who applied the Polaroid color-translating ultraviolet microscope to the study of normal and diseased glomeruli. They found that the nodules of intercapillary glomerulosclerosis, and in fact the glomeruli of diabetic kidneys without typical nodules, showed a remarkably distinctive and apparently specific

Fig. 14.—Another cortisone lesion in glomerulus of rabbit kidney. Here the hyaline mass appears to lie within the lumen of a capillary, and red blood cells are clearly visible within it. From slide kindly furnished by Dr. J. M. B. Bloodworth, Jr.

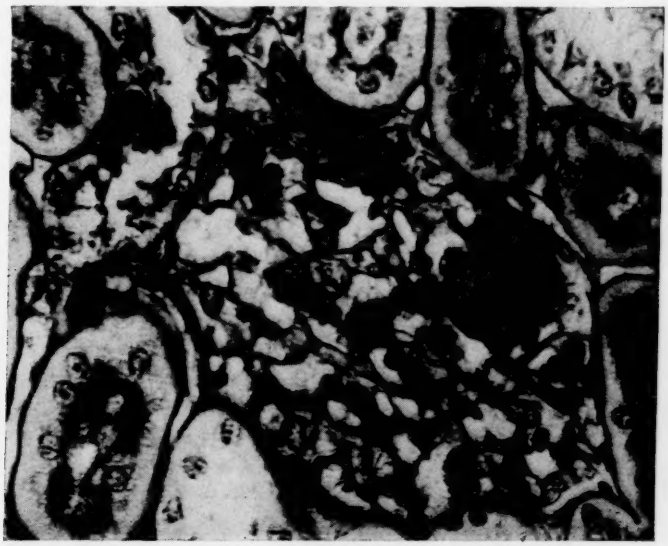

Fig. 15.—Two hyaline, apparently intracapillary masses staining deep red with periodic acid and Schiff reagent. Cortisone-injected rabbit.

ultraviolet absorption pattern. They attributed this finding of a distinctive pattern, which seemed to apply, although less strikingly, to other diseases as well, to chemical variations in the protein and mucoprotein components of the tissue. In contrast to this striking variation and apparently characteristic pattern for different glomerular diseases is their more recent study of arterioles,[127] which showed a remarkably uniform ultraviolet absorption pattern of the arterioles in different diseases. This evidence suggests, then, that the substances making up the hyaline material in the glomeruli have a different physicochemical constitution from the hyaline of diseased arterioles.

These findings perhaps lend some support to the thesis that the hyaline material in intercapillary glomerulosclerosis represents in essence an accumulated deposit of substances circulating in the blood stream, perhaps on the substrate of a damaged basement membrane. Such substances could be, at least in part, lipids, according to Wilens.[158] McManus[129,130] suggested that they might be mucopolysaccharides, deposited from the circulating blood, and this suggestion has achieved considerable popularity. Friedenwald[22,195,196] has used it to embrace diabetic retinopathy as well (see later) and has tried to link it with elevated levels of serum mucopolysaccharides. It has been extended still further, to suggest that most of the histopathologic manifestations of diabetes may be explained on the basis of altered metabolism of either simple polysaccharides, such as glycogen, or more complex ones, e.g., mucopolysaccharides and glycoproteins.[23]

The question then arises as to whether there actually is an elevation of mucopolysaccharides in the blood in diabetes. Berkman and co-workers[24,25] have tried to answer this, measuring the concentrations of polysaccharides bound to serum protein, and of serum glucosamine in normal controls, in nondiabetics with renal disease, and in diabetics with and without demonstrable vascular disease. They found significant elevation of these substances in the serum in diabetes, but only when clinically detectable vascular disease was present. These results are most interesting, but will require further extension to be sure that the elevated polysaccharides are not a result, rather than a cause, of the vascular disease. Of particular interest is one autopsied case[25] of a diabetic patient who had one large hypertrophied kidney showing severe intercapillary glomerulosclerosis and one small atrophic kidney (from occlusion of the main renal artery) which showed no lesions in any of many glomeruli which were examined, and hardly any hyaline arterioles. This case suggests that either feeble blood flow or low pressure prevented the deposits which affected the other kidney.

Gilliland and associates[197] found a progressive rise in total protein-bound polysaccharides with increase of diabetic complications, and a considerable change demonstrable before any clinical symptoms. They found most of the change in the alpha-2 globulin fraction, less in the beta fraction, with no evidence of an abnormal polysaccharide. They concluded that the protein and protein-bound polysaccharide electrophoretic patterns were characteristic in the Kimmelstiel-Wilson syndrome, and found a similar pattern in amyloid disease. They thought that their results tended to support the suggestion that the protein-bound polysaccharides in the lesions might be of hematogenous origin.

Keiding and Tuller[198] found a general increase in the concentrations of the nonhexosamine and hexosamine components of a total serum protein precipitate

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and of a mucoprotein fraction of the serum of diabetics as compared with nondiabetics. These findings are apparently related to the recognized decrease of albumin and increase in alpha-2 globulin in diabetic patients.[199-202] Their data differed from those of Berkman in that they found an increase in diabetics without obvious complications as well as in those with nephropathy. Similar results were obtained by Nielsen and Poulsen.[203]

The significance of the "exudative" lesion described previously is obscure. It seems to appear rather late, and since, as Anderson[170] observed, there is never any evidence of repair, it is perhaps best regarded as a late event, perhaps a relatively nonspecific manifestation of the nephrotic syndrome, and perhaps not an integral part of the Kimmelstiel-Wilson lesion.

The interpretation of the experimental lesions produced with cortisone is difficult. The usually intracapillary location of the hyaline material makes its relationship to the classical hyaline nodule rather questionable. At present it is difficult to follow the tentative suggestion of Bloodworth and Hamwi[182] that the intracapillary deposits may eventually diffuse into the intercapillary space to form lesions more characteristic of the human disease. However, the results of long-term experiments which these authors have in progress[204] will be of great interest.

It should also be noted that Anderson[170] has maintained, apparently mainly on the basis of shape of the lesions, and on the occasional presence of red cells, that the nodular lesion of the human disease probably begins as an intracapillary coagulum. It is difficult to imagine the mechanism of such a transformation.

Any attempt to apply the experimental cortisone lesions to the interpretation of human disease naturally raises the question of whether there is evidence for overactivity of the adrenal cortex in cases of diabetes mellitus in man. Here again there are conflicting opinions. Although some writers have found essentially normal urinary corticoid excretion,[205-207] no definite increase in adrenal size in uncomplicated diabetes,[23,208] and even evidence of a diminished cortical reserve,[209-211] others reported rather marked increase in excretion of both 11-oxysteroids and 17-ketosteroids in cases of intercapillary glomerulosclerosis and retinopathy.[212,213] Whether, if this is confirmed, it is to be regarded as cause or effect is still to be settled. The uncertain effects of adrenalectomy[214,215] and hypophysectomy[216] do not clarify the situation. If intercapillary glomerulosclerosis were the result of overactivity of the adrenal cortex, one would expect it to be reported in cases of Cushing's syndrome. Lesions resembling it are said to have occurred in two patients given intensive ACTH or cortisone therapy.[187] Most interesting, perhaps, is the recent demonstration by Sommers[216a] that the same ultraviolet absorption pattern found by him in diabetic glomeruli[128] may be detected in the glomeruli of patients or animals treated with cortisone. In summary, it may be said that the evidence that intercapillary glomerulosclerosis may be due to adrenocortical overactivity is slender, as is acknowledged by proponents of the hypothesis.[213,217] Discussion of the relation of the adrenal cortex to diabetic retinopathy will be found later.

Diabetic Retinopathy.—

1. *Description of the vascular lesions:* For many years ophthalmologists have recognized, in cases of diabetes, an ophthalmoscopic picture characterized

by small, punctate, or irregular hemorrhages, dilatation and tortuosity of retinal veins, and "hard, white exudates," often ending in the distressing and disabling condition known as retinitis proliferans.[218] The minute hemorrhages were emphasized in the classic paper of Waite and Beetham,[219] who called attention to the fact that retinal disease in diabetes should be regarded as involving primarily the capillaries and venules rather than the arterioles. Later Elwyn[220] described what he called "prestasis," meaning a dilatation of capillaries with consequent slowing of the blood flow, as a fundamental feature of the condition.

For many years the small punctate "hemorrhages" were regarded as perhaps the most characteristic feature of diabetic retinopathy, especially in its early stages. They were considered to be hemorrhages in spite of their tendency to remain in one place for long periods without being absorbed.[221] Recently it has been recognized that many of these persisting punctate red spots are actually the capillary microaneurysms described in 1879 by Nettleship in a case of "glycosuric retinitis" reported by MacKenzie.[223] These aneurysms were rediscovered by Ballantyne and Loewenstein,[224] who described them as 30 to 90, usually 50 to 60 microns in diameter and located chiefly in the perimacular region. Ballantyne[225] described them also in flat, unstained preparations of retina and in histologic sections, where they may have thick, hyaline walls.

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Fig. 16.—Retinal microaneurysms. Flat mount of retina, stained with periodic acid, Schiff reagent method according to Friedenwald. Same patient as in Figs. 2 and 4.

The next advance in the study of the subject was made by Friedenwald,[226] who, with brilliant success, applied the Hotchkiss-McManus technique to whole preparations of retina, stained entire and mounted flat. This method brought out the tiny saccular aneurysms with a clarity which had not been achieved before and showed without any doubt that they actually arose from capillaries and were not small endothelized extravasations of blood (Fig. 16). He also showed that some of the aneurysms had thick, hyaline walls, and speculated as to whether a capillary aneurysm which becomes pale under repeated ophthalmoscopic examination may not be undergoing hyalinization. Sometimes a laminated appearance can be seen with silver stains, suggesting that the hyaline material may be laid down in successive episodes.[227]

The punctate spots are usually described as on the venous side of the capillary. Along with the microaneurysms, some dilatation, tortuosity, and beading of the retinal veins are commonly described, and some authors have emphasized the occurrence of phlebosclerosis[228,229] (Fig. 4). "Venous varices" of the retina are described as common in diabetes.[230] The importance of this apparent relationship between venous stasis and microaneurysms is brought out by Becker and Post,[231] who found retinal aneurysms in all of thirty-nine eyes in which occlusion of the central vein was present, and also produced them experimentally in cats (see later).

2. *Specificity of microaneurysms:* It is generally agreed that capillary microaneurysms of the retina are "characteristic" of diabetes. However, their specificity for this disease seems to be considerably less than that of intercapillary glomerulosclerosis. They have been found in nondiabetic patients in various disease states, particularly malignant hypertension,[232] but also in various other conditions.[233-235] Ashton[227,233] has carried out extensive investigations by injection methods, by which he claims to find more aneurysms than by other means. He has found them in various diseases and even in "normal" eyes, a fact for which no explanation is offered. A question may perhaps be raised as to whether the "beaded" type which he illustrated[234] is a true aneurysm, and whether it might be an artefact of the injection technique. Ashton denied the latter possibility.

There seems to be disagreement on the question of whether, and how often, capillary aneurysms may appear in tissues other than the eye. Friedenwald[22] found them in only three of forty cases in which he examined the nail beds, also a single aneurysm in an investigation of ten brains of patients who had diabetic retinopathy. Some divergence is found in studies of the conjunctival capillaries, some workers[236,237] reporting aneurysms in 55 per cent of diabetics, Friedenwald[22] considerably fewer. The extensive searches of various tissues by Ashton[227] have shown aneurysms only in the renal glomeruli in cases of diabetic retinopathy. The presence of these supposed aneurysms of the glomerular capillaries constitutes a reason for suggesting that the pathologic process may be similar in the eye and the kidney.[22,195,238]

3. *Experimental production of aneurysms:* Becker and Post[231] described and illustrated microaneurysms of the retina produced by heat coagulation of the central retinal vein with an inserted wire in cats. This would seem to suggest that the aneurysms are readily produced by mechanical means. Becker[188] has found aneurysms in the retina of rabbits given large amounts of cortisone. Others[191] have not been able to duplicate the cortisone lesions.

4. *Pathogenesis:* As noted previously, mechanical factors appear to play an important part in the production of capillary aneurysms in the retina, if one is to judge from the effects of occlusion of the central retinal vein.[231] Whether such mechanical factors combine with some unknown aspect of the diabetic state, such as a "weakness" of the vessel wall, is unknown. Certainly diabetic retinopathy seems to be more closely related to duration of diabetes than to severity of the disease.[221,239]

An increase in capillary fragility is common in diabetic retinopathy;[240-243] however, the vessels in which fragility is demonstrated by the tourniquet test are not those which show aneurysms; also it does not necessarily follow that a weakness which predisposes to rupture of the wall will also predispose to aneurysm formation. Attempts to improve the retinopathy by treating the capillary fragility with various drugs have been disappointing.[244,245] Theories postulating a circulating "toxin" seem to be without foundation, although anoxia might be considered a cause of weakening of the capillary wall.[221]

One possible explanation for the presence of aneurysms in the kidney (if they do occur there) and retina, and one not usually mentioned in the literature, is that the capillary pressure is presumably higher in these two locations than anywhere else in the body. The pressure in the glomerular capillaries is accepted as higher than that in most other capillaries[246] and the fact that the intraocular tension represents the highest tissue pressure in the body indicates that the pressure in the retinal capillaries must also be high, perhaps the highest in the body.[247] The anatomic arrangement of the capillaries may also be a factor.[247a]

Friedenwald,[22] noting some similarity between the retinal aneurysms and the lesions of intercapillary glomerulosclerosis, took up the suggestion of McManus[129] involving deposition of mucopolysaccharides from the blood stream and extended it to cover both types of lesions. It is perhaps noteworthy that many of Berkman's[25] patients with renal disease and high polysaccharide levels also had retinopathy. Unfortunately, one is forced to wonder whether the high levels of polysaccharides in these cases might not be secondary to the renal disease, as has been suggested in the case of the elevated lipoproteins and cholesterol in such cases.[53]

The relationship between the retinal and the renal lesions in diabetes is uncertain. Certainly the two types of lesion tend to be associated with one another, but this is not invariably so. It is also true that both appear to contain mucopolysaccharides, which may well be hematogenous deposits.[25,197] There are, however, distinct morphologic differences between the two, and it is probably an oversimplification to regard the renal lesion as a "hyalinized saccular aneurysm."[196]

Evidence linking the adrenal cortex with diabetic retinopathy as well as with renal lesions is exciting current interest. Much of the previous discussion under intercapillary glomerulosclerosis also applies to the consideration of the retina. The presence of retinal lesions in patients taking corticotrophin,[189] and undergoing pregnancy,[248] if confirmed, may be significant, but observations on the vacuolation of the adrenal cortex and on stressful situations in general involve so many variable factors that no clear conclusions can be drawn as yet. The apparent reversal of diabetic retinopathy following onset of Simmonds' disease is a remarkable and perhaps highly significant finding.[249] Yet the results of adrenalectomy[214,215] and hypophysectomy[216] are unclear. For instance, the improvement in retinopathy noted in two cases[214] may have been due to the associated drop in blood pressure, especially in view of the fact that improvement was not noted in two cases of the same series in which the blood pressure did not fall.

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Becker and co-workers[189] made a lengthy plea for possible interaction of the adrenal cortex and B-vitamins in the pathogenesis of diabetic retinopathy and glomerulosclerosis. They pointed out that, while diabetics without retinopathy often show a decrease of adrenocortical function, those with retinopathy may show an increase. They also presented evidence suggesting a higher average adrenal weight and greater incidence of vacuolization of the zona fasciculata in patients with Kimmelstiel-Wilson lesions as compared to diabetics without such lesions. They found further that pantothenate would "normalize" the eosinopenic response to corticotropin in diabetics without retinopathy and suggested that a deficiency of this vitamin may account for lowered adrenal function in these patients. They further cited work showing that cortisone increases the turnover of vitamin B-12 in the body and that diabetics with retinopathy excrete much more vitamin B-12 in the urine (in a vitamin B-12 tolerance test) than either diabetics without retinopathy or nondiabetics.[250] These data they interpreted as indicating an overfunction of the adrenal cortex in diabetics with retinopathy.

These authors went on to cite work suggesting that the adrenal cortex may be involved in the metabolism of mucopolysaccharides and of lipoproteins[251-253] and that vitamin B-12, on the other hand, has lipotropic properties.[254-256] They concluded that "at present there is no outstanding evidence to negate the tentative working hypothesis of a role of relatively increased function of the adrenal cortex in the pathogenesis of this disease complex."[189]

Obviously, much more evidence will be required to test the validity of these various hypotheses, to ascertain, for instance, whether the apparent overactivity of the adrenal cortex in some cases may not be a nonspecific secondary stress effect rather than an integral part of the disease process.

DISEASE OF SMALL VESSELS IN OTHER TISSUES

Scarcely any information is available on the presence or absence of lesions of the smallest blood vessels in tissues other than the kidney and the retina. This might be explained by a special susceptibility of these two organs, because of higher capillary pressure or for some unknown reason. It might also be due to inadequacy of present methods. As noted previously, search for capillary microaneurysms in tissues other than the eye has not been particularly rewarding. Ordinary histologic techniques have offered little.

The observations of Ditzel[257-259] suggest that methods may be of prime importance in the study of disease of the small vessels. By microscopic study of the conjunctival vessels in living patients, he has described what he considers to be characteristic patterns of dilatation, angulation, tortuosity, and the like in the capillaries and venules not only of diabetics but of their relatives and children. These results, if confirmed, will have important implications, not only with regard to the extent of disease of the small vessels in the diabetic, but also with relation to the question of whether the vascular alterations precede or follow the obvious metabolic disturbances of the disease (see later).

Mendlowitz and co-workers[260] found decreased hallucal circulation in diabetics by a calorimetric method. Another interesting study, which will also

require confirmation, is that of Megibow and associates,[261] who measured the digital circulation in young diabetics by microplethysmographic methods and found apparently significant differences, interpreted as evidence of occlusive disease of the small vessels, between about one-half of these patients and non-diabetics. Since no histologic correlation was available, these authors were unable to state whether the supposed lesions might be in arterioles, capillaries, or venules. The authors' data do not show how early in the disease such changes were found, since they stated that all their patients had been observed for their diabetes for "extended periods." Even aside from possible questions of technique and interpretation, it is not clear that their data necessarily lead to the conclusion that "the intrinsic vascular abnormality of diabetes mellitus is an occlusive lesion of the minute blood vessels" or that the increased proximal resistance assumed to result from these lesions may account in part for the increased incidence and accelerated development of arteriosclerosis in diabetes. Nevertheless, a combination of their methods and those of Ditzel,[257-259] applied to diabetic and "prediabetic" patients, might yield much valuable information, especially in relation to the question of whether the vascular lesions precede or follow the recognizable metabolic disturbances of diabetes.

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RELATION OF THE DIABETIC STATE TO THE VASCULAR LESIONS

There are three possibilities:[262]

1. Vascular disease might cause diabetes.
2. Diabetes might cause vascular disease.
3. Some common factor might cause both the diabetes and the changes in the blood vessels.

As regards the first possibility, Moschcowitz[121] seems to be the only recent writer to maintain that vascular disease causes diabetes in any significant number of cases. He holds that hyalinization of the islands of Langerhans is a result of vascular sclerosis involving capillaries[263] as well as arterioles and that in this sense vascular disease is a cause of diabetes in the older age group. Since hyaline islands of Langerhans may occur in the absence of arteriolar sclerosis in the pancreas, and since severe vascular disease of the pancreas may be present without diabetes, the hypothesis seems a doubtful one.[23]

The second possibility, i.e., that the metabolic disturbances of diabetes are the cause of the vascular lesions, so that the latter are "complications" of diabetes, is, of course, widely accepted and the basis for efforts at preventing vascular disease by careful control of the diabetes. The correlation between duration of diabetes and appearance of vascular lesions gives it support.

The third possibility, that both the diabetes and the vascular lesions may be the result of some other factor, so that the blood vessel changes are "concomitants" rather than "complications" of the diabetes, is one that must be seriously considered. It is entirely possible, for instance, that the vascular disorders are genetically associated with, but otherwise unrelated to, the diabetes. Thus a hereditary factor for "defective" blood vessels might be linked to the

factor producing diabetes.* Or, some common factor, possibly endocrine, such as excess adrenal cortical hormones, might cause both the diabetes and, by an unrelated mechanism, the blood vessel changes.

Actually, as Ricketts[267] pointed out, there is practically no direct evidence on this general subject. He cited Lawrence[268,269] as having seen vascular lesions in cases of diabetes produced by such causes as chronic pancreatitis[270] and hemochromatosis. As far as I know, there is hardly any literature on this particular point, and certainly such cases should be collected to fortify the evidence. Marble and Bailey,[271] in a fairly extensive study of hemochromatosis, recorded no vascular lesions of the type characteristic of diabetes. Hudson[272] found retinal lesions in one case. To support the "complications" hypothesis, Ricketts[267] cited various vascular lesions which have been described in experimental animals. However, as has been emphasized in several places in the previous discussion, it is by no means clear that duplicates of the human lesions have been produced in animals by diabetes alone. Many of the lesions so described leave much to be desired as far as resemblance to the human lesion is concerned. Nor is it clear that adrenal cortical or pituitary hormones supply the lacking factor.

The observations of Ditzel,[257,258] cited previously, suggesting that alterations of conjunctival vessels may be apparent not only before clinical diabetes is manifest, but even in the children of diabetics,[259] could, if confirmed, constitute extremely important evidence.

The elevation of serum lipids (especially cholesterol, lipoproteins, and fatty acids) sometimes seen in diabetes, and the elevation of mucopolysaccharides found in connection with the capillary lesions, suggest, of course, a causal connection between these metabolic aberrations and the disease of the blood vessels. It is particularly tempting to suggest[23] that all the major pathology of diabetes may be explained in terms of disturbances of carbohydrate metabolism, affecting not only the simpler polysaccharides such as glycogen but the more complex mucopolysaccharides that are components of the ground substance of connective tissue and blood vessel walls.† However, the association could be fortuitous (or genetic) and at present there are no means of proving a cause and effect relationship.

The difficulties just mentioned doubtless provide much of the basis for the current dispute concerning the importance of meticulous control of the blood sugar in preventing vascular damage. It is generally agreed that the vascular disease increases in severity in direct proportion to the duration of the diabetes, although there are exceptions. Yet those who hold that rigid control is necessary[1,6,8,241,274,275] are still opposed by those who claim no worse results with "free diet."[276-279] Many of the equivocal differences in vascular disease in patients with "good" versus those with "poor" control are explained on the basis that all control is inadequate.[280] If it could be clearly shown that degree of control had no relation to the present appalling incidence of vascular "complications" in young

*Such a hypothesis would be consistent with what is known of the genetics of diabetes.[264] An example of a single gene influencing several tissues, including blood vessels, is Marfan's syndrome.[265,266] An example of a metabolic disorder associated with blood vessel disease is familial xanthomatosis.[23,49,59]

†This suggestion has unfortunately been somewhat misinterpreted[273] to mean that glycogen deposits may be irreversible and hence lead to the "degenerative" changes—a point of view that was not intended.

diabetics of long duration,[281-283] considerable support would be given to the theory that the "complications" are really "concomitants," i.e., part of the disease.[152] Unless and until such demonstration is available (and there is much evidence on the other side), it would seem wise to use "the only weapon we possess, imperfect as it is—the careful control of blood sugar."[267]

CONCLUSIONS

1. Diabetes mellitus is associated with a high incidence of vascular disease involving large and small arteries, capillaries, and venules.

2. Disease of the large arteries (atherosclerosis, medial calcification, intimal fibrosis) in diabetes does not seem to differ in kind from that seen in nondiabetics, but is often more severe in diabetics. This is especially striking in females.

3. Disease of the capillaries, especially those of the kidney and the eye (perhaps because of higher pressure in these organs), with deposits of a hyaline, polysaccharide-containing substance, is so characteristic of diabetes as to be almost pathognomonic. Modern techniques suggest that the deposits have a distinctive physicochemical constitution.

4. Recent literature has given considerable space to the so-called "exudative lesion" in intercapillary glomerulosclerosis. The specificity and significance of this finding are in doubt.

5. The vascular lesions of diabetes mellitus have not been reproduced unequivocally in experimental animals, in the sense of having been induced by the diabetic state alone. Those lesions that have been described, especially in the kidney, cannot be regarded as an exact duplicate of the human lesion. Something like the "exudative lesion" in the kidney, and perhaps retinal microaneurysms as well, can be produced in rabbits with large doses of cortisone.

6. Vascular lesions in diabetes mellitus are accompanied sometimes, but not always, by elevations of the serum levels of cholesterol, lipoproteins, and esterified fatty acids, also (especially the late capillary lesions) by elevated serum polysaccharides. Whether any of these have a causal relation to the vascular lesions is uncertain. It is conceivable that a fundamental disorder of carbohydrate metabolism in diabetes may affect the polysaccharide-containing ground substance of blood vessels of various sizes in such a way as to predispose to the lesions.

7. Recent evidence involving overactivity of the adrenal cortex and the metabolism of vitamin B-12 in the pathogenesis of the vascular lesions requires further evaluation.

8. It is uncertain whether the vascular disturbances are related to the diabetes genetically or by way of some other common factor, i.e., as concomitants, or causally, i.e., as complications. The fact that the vascular lesions tend to increase in severity with duration of the diabetes suggests that the second hypothesis may be true, and on this basis careful control of the diabetes may tend to prevent the lesions.

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Editorials

THE PROBLEM OF SHOCK IN MYOCARDIAL INFARCTION

Shock occurring in the course of acute myocardial infarction is a condition not easy to define in precise terms, either clinical or physiologic, but its importance for prognosis and treatment is fully recognized. Reports from many clinics in recent years[1-4] have concurred in the finding that the mortality in patients with myocardial infarction who have suffered shock of significant extent and duration is high, usually between 50 and 80 per cent.

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As a clinical situation, shock in myocardial infarction is fairly easy to identify. Type of onset and course will vary greatly from case to case. Selzer[5] described four forms: (1) blood pressure fall, sometimes for several hours, with spontaneous recovery; (2) progressive hypotensive shock with fatal termination; (3) shock associated with cardiac arrhythmias; (4) a period of hypotension, followed by recovery, followed in turn by a second, progressive, and fatal episode. In general, the blood pressure is a good index, or at least a good warning sign. In the milder cases of Selzer's Group 1, there may be no further clinical evidence of shock, but usually, with hypotension below 90/70 or thereabout for more than one or two hours, the clinical picture of shock will develop, sometimes very suddenly: weakness, pallor, sweating, ashen cyanosis, small thready pulse, cold extremities, clouded or anxious mental state, with or without actual cardiac pain. Most often, definite manifestations of heart failure will be present also: dyspnea, orthopnea, poor heart sounds, venous congestion, frequently frank pulmonary edema. Pulse rate is commonly rapid, but may be slow. The immediate cause of such an episode may be apparent: an extension of the infarction shown by electrocardiogram, a pulmonary embolus and infarct, an acute arrhythmia, such as atrial fibrillation, less often supraventricular or ventricular tachycardia. At other times no definite cause is found.

Of the dynamic and metabolic changes in myocardial infarction with shock, recent studies have added considerably to our knowledge, although much remains unknown. Cardiac output, as determined by the dye injection technique, falls markedly, to 1.5 or even 1.0 L. per minute per square meter of body surface.[6,7] The correlation between drop in cardiac output and degree of shock is close, even better, in some series, than the correlation with arterial blood pressure.

Exact figures on arterial oxygen saturation are few. Borden, Ebert, and Wilson[8] found that in seventeen patients without pulmonary edema or shock, arterial oxygen saturation was normal, whereas in five patients with pulmonary edema and one in manifest shock, the unsaturation was marked, averaging 80.8 per cent. Arterial blood pH and CO_2 tensions in all these cases were within normal limits. Measurements of pulmonary arterial pressure are largely want-

ing, because of the justifiable reluctance of investigators to catheterize the heart in these patients. Presumably, in cases with pulmonary congestion or frank pulmonary edema, pulmonary vascular pressures are increased.

Venous pressure, an index of right-sided congestive failure, is variable, sometimes very high, more often moderately elevated, 100 mm. to 150 mm. H_2O, not infrequently normal, rarely really low. Blood and plasma volumes are also variable, most often either normal or somewhat increased.[6]

So-called peripheral resistance, that is, the mean arterial pressure divided by the cardiac output (times 1,332, a constant), is almost always increased, as it is in most forms of clinical shock (also in most forms of congestive heart failure).

The nature of the state of shock in myocardial infarction has been much discussed, as to whether it is largely true shock—peripheral vascular collapse—or largely congestive failure. Perhaps the strongest argument for the latter position was that of Stead and Ebert[9] some years ago, who stated that in the obvious presence of congestive heart failure, the term "shock" should not be used at all. While it is true that frank left-sided or left- and right-sided heart failure often dominates the clinical picture, other features are clearly different from those seen in most instances of congestive heart failure: low arterial blood pressure, peripheral ischemia rather than congestion, and the obvious evidences of acute and severe inadequacy of blood flow to tissues—beyond that encountered in the congestive state—which are so typical of peripheral vascular collapse. It seems both probable and reasonable that both processes are occurring together: myocardial insufficiency with congestive failure; and peripheral circulatory failure, with vasomotor disorganization and inadequate perfusion of vital organs—the key phenomenon in the "shock" state.[10,11] The relative dominance of one form of failure over the other will vary from case to case.

The management of shock in myocardial infarction is a complex affair, involving many types of procedure, requiring also constant change and readjustment as the clinical situation alters. The basic measures for acute heart failure: digitalis, oxygen, sedation, or narcotic as needed, and later diuretics, are fully indicated in the added presence of shock. The use of anticoagulants in this group of myocardial infarctions is also generally accepted.[12] In cases of shock with no evidence at all of congestive failure, digitalis may not be needed. The only serious hazard in the use of digitalis in these cases is its tendency to increase heart muscle irritability: it may have to be withheld in the presence of certain acute arrhythmias. This is sometimes a difficult clinical decision. The effectiveness of oxygen by tent or mask, in clearing cyanosis and relieving dyspnea, is unquestioned. Godfrey, Pond, and Wood[13] demonstrated by oximeter considerable improvement in arterial oxygen saturation following oxygen therapy, in a small group of cases of myocardial infarction.

Somewhat more controversial is the use of positive pressure expiration (up to 4 or 5 cm. H_2O) by mask, for pulmonary edema. This has been used for over five years on our service at Bellevue Hospital, with regularly beneficial effects in clearing pulmonary râles, often within thirty to sixty minutes. It is not known

whether this occurs by producing a counterpressure at the alveolar-capillary surface, or (more likely) by increasing the total intrathoracic pressure, thus providing a sort of body tourniquet effect at the outer limits of the chest cage.[14]

The use of plasma, or blood transfusions, or arterial transfusions, when shock deepens and does not respond to other measures, is also controversial.[15] I concur with most recent reports which do not favor these procedures.[16] Venous return is almost always adequate, and the heart dilated; the difficulty is cardiac emptying and not cardiac filling.

An important recent addition to counter the shock is the use of sympathicotonic drugs, intravenously, with nor-epinephrine the most favored agent, when arterial pressure continues to fall, or disappears.[16-18] Diastolic pressure is essential for coronary flow, and nor-epinephrine or a similar agent provides the needed pressure rise, through peripheral vasoconstriction, with a minimum of increase in cardiac work: there is no increase in cardiac output or tissue oxygen consumption, and the pulse rate is but little altered. Arterial systolic pressure is maintained around 100 to 110 mm. Hg by carefully controlled continuous infusion. The risk of producing a damaging arrhythmia through irritation of heart muscle seems not to be a serious consideration clinically. The chief hazard is sloughing and necrosis along the injected vein site if the infusion of nor-epinephrine is continued over periods of days, as is sometimes necessary.

Summarizing, it may be concluded that myocardial infarction with shock produces in most instances a combination of true acute congestive heart failure, and true peripheral vascular failure, and that effective management requires treatment of both conditions.

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CYSTIC FIBROSIS OF THE PANCREAS

(Fibrocystic Disease of the Pancreas; Mucoviscidosis)

Dramatic reductions in death rates from acute illnesses of infancy and childhood have served to heighten interest in chronic diseases in the younger age group. Preventive and therapeutic triumphs attributable to improved nutrition, immunization, antibacterial agents, and newer knowledge of supportive treatment have greatly lessened the threat of acute diseases. Thus, the chronic diseases of childhood now loom larger in importance than formerly and represent a hard core of resistance.

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One of the most challenging chronic diseases in pediatric practice is cystic fibrosis of the pancreas, also termed fibrocystic disease of the pancreas, or mucoviscidosis. Its importance is exemplified by the fact that it afflicts approximately 1 of every 1,000 liveborn children and that it is found as the chief cause of death in about 3 per cent of unselected autopsies performed on children. In pediatric circles it has attracted much attention in recent years not only because of its frequency but also because of its familial background, severity, variation in clinical picture, and the introduction of new diagnostic procedures and improved methods of management. Yet many children with this condition are still undiagnosed and thereby fail to receive the benefits of proper treatment.

Based on the frequency with which cystic fibrosis of the pancreas often affects more than one child in a family, the current concept is that the condition is transmitted according to Mendelian laws by a recessive gene. It is not uncommon to find two or more cases in the children of one family. I now have a patient under my care who is the fifth affected child in a family of 8 children, 4 of whom have already died with cystic fibrosis of the pancreas. The other 3 are normal.

Although recognized as an hereditary disorder, the nature of the defect that is transmitted remains obscure. Because of the increased viscosity of pancreatic secretions and the mucus of the tracheobronchial glands, as well as certain other glands, it has been postulated that the inherited abnormality involves mucolytic enzymes. Another interpretation (Farber) based on abnormal viscosity of mucus at the sites mentioned is that the disease represents a neurogenic imbalance in which parasympathetic (vagal) stimulation is excessive. Still another viewpoint (Andersen) is that the pancreatic abnormality is hereditary, but that the pulmonary changes are due to nutritional changes occasioned by the pancreatic insufficiency.

The two organs most severely affected by this disease are the pancreas and the lungs. The typical patient has a combination of digestive disturbances owing to the pancreatic lesion and protracted pulmonary obstruction and infection caused by the changes in the lungs.

The pancreas produces an unusually viscid juice which obstructs its ducts and acini, leading to cystic dilatation of the acini, which become distended with homogeneous, eosinophilic, inspissated material. There is eventual atrophy of the pancreatic parenchyma (except for islet cells), associated with diffuse pancreatic fibrosis.

The tracheobronchial glands produce an abnormally viscid mucus which obstructs the finer air passages and makes it difficult for the lungs to rid themselves of infection. Patchy areas of atelectasis occur, or even lobar atelectasis, and generalized obstructive emphysema is a common finding. With high frequency the *Staphylococcus aureus* establishes itself in the lungs, where it sets up a chronic infection of a rather indolent, but at times more active, nature in the bronchi and peribronchial tissues, usually without a tendency to septicemia. Smaller bronchi and the bronchioles are distended and filled with mucopurulent exudate which predisposes to atelectasis and emphysema. The bronchial walls also become inflamed and peribronchial inflammatory areas occur, which at times coalesce to form zones of chronic pneumonitis. Fibrosis of a marked degree may occur throughout the lungs, as well as bronchiectasis. Metaplasia of the tracheobronchial mucosa may result from vitamin A deficiency caused by failure to absorb fats properly. However, this latter lesion has become infrequent since the widespread use of generous quantities of water-miscible polyvitamin preparations in the management of these patients.

Secretions in a number of other locations may be abnormal. At times the gall bladder is small and the glands are obstructed with viscid mucus. Intrahepatic biliary ducts may become obstructed by viscid material and this may lead to hepatic cirrhosis. Brunner's glands in the duodenum likewise may produce abnormally thick mucus, as may the glands of the esophagus and jejunum. The salivary glands may also show obstruction and dilatation by thick secretions. Of marked clinical interest is the recent demonstration that these patients tend to lose 2 to 4 times the usual amount of sodium and chloride in their sweat, as well as excessive quantities of potassium. Therefore, they tend to suffer hyponatremia and hypokalemia much more frequently than normal children do, especially during hot and humid weather.

With this understanding of the principal basic mechanisms of the disease, it becomes easier to grasp the significance of the clinical manifestations, which are related largely to the pancreatic and pulmonary lesions.

Owing to marked decrease or total absence of pancreatic enzymes in the newborn infant with this disease, an abnormal meconium results which is so thick and mucilaginous that it cannot be propelled properly by peristalsis. The abnormal meconium produces intestinal obstruction and the entity is known as meconium ileus. Perforation of the bowel, resulting in meconium peritonitis, may occur before or after birth, and volvulus has been noted in some patients. Meconium ileus may be suspected when there is observed: (a) failure of the infant to pass meconium; (b) abdominal distention; (c) palpation of thick, doughy, cordlike masses in the area of the lower ileum; or (d) roentgenographic findings of stippling in the terminal ileum, and demonstration of multiple opaci-

ties scattered throughout the peritoneal cavity caused by calcification which occurs rapidly when perforation leads to meconium peritonitis.

Operation is mandatory at this stage, but still carries an exceptionally high mortality, despite excellent supportive care and good surgical technique. The ileum is opened and an attempt is made to remove the mucilaginous meconium manually, or by means of irrigations with saline solution. Pancreatin solutions have been used, but would appear to be more beneficial if employed after the bowel is closed. Resection of the involved terminal ileum and the establishment of a double-barrel ileostomy through which the bowel may be irrigated with pancreatic ferments may prove successful. If the patient survives, he faces the hazards of the other manifestations of cystic fibrosis of the pancreas. Fortunately, meconium ileus occurs in only about 10 per cent of patients with fibrocystic disease of the pancreas.

Patients who escape meconium ileus—the earliest of all evidences of cystic fibrosis of the pancreas—vary in the nature of onset of clinical manifestations. (a) Some have obvious digestive abnormalities which lead to the proper diagnosis; (b) others have early onset of pulmonary trouble without evident digestive difficulties; whereas (c) the majority have a combination of digestive and respiratory manifestations. Although the experienced clinician should be able to suspect the diagnosis on either digestive or pulmonary grounds, the condition almost declares itself when the combination exists.

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One of the earliest findings, present in a large proportion of cases, is failure to regain the birth weight in the expected time. Two-thirds of the patients gain weight very slowly for one to three months after birth. They tend to develop wasted buttocks and protuberant abdomen which result in a characteristic appearance. Longitudinal growth also is retarded early in the disease.

The appearance of the stools may or may not give a ready clue to the proper diagnosis. Unfortunately, it is too generally believed that the stools are always large, mushy, fatty, and foul. Actually, individual stools may not appear very abnormal, although they are usually unformed. The main point is that the total daily fecal bulk is increased, owing especially to loss of large amounts of unabsorbed fat and protein. The weight of feces excreted daily is about three times normal. When solid foods are added to the diet the stools are more apt to become typically bulky, mushy, frothy, fatty, and foul. At such times the odor of the stool may be unbearable. These patients may have bouts of severe diarrhea, but they are not so prone to this as are children with idiopathic celiac disease.

Unless pulmonary infection is present the appetite is usually ravenous. May and Lowe showed that children with cystic fibrosis of the pancreas on unrestricted diets ate about one and a half times as much as normal persons. Thus, the presence of excessive appetite in the presence of stools of the type mentioned above suggests the diagnosis. Even though there is considerable wastage of fat and protein in the stools in this disease, it has been shown that the patients are capable of absorbing approximately 60 per cent of the ingested fat and protein nitrogen. By increasing food intake they may therefore ingest enough to have a total daily absorption of these substances that equals that

of the healthy child. Thus, provided pulmonary infection does not interfere with appetite, they may even gain weight well despite abnormally large fecal losses of foodstuffs.

Certain vitamin and mineral deficiencies may be caused by abnormal stool losses. Fat-soluble vitamins A, D, and K are absorbed poorly. Vitamin A deficiency with keratinizing metaplasia of tracheobronchial membranes was formerly considered the sole cause of the pulmonary manifestations of this disease, but is now regarded as incidental to the pancreatic insufficiency and not the basic cause of the respiratory difficulties. In fact, it has now become less common since administration of water-miscible polyvitamin preparations has become standard practice for these patients. Vitamin D deficiency may lead to osteoporosis. However, rickets is rarely seen, since growth retardation, so characteristic of cystic fibrosis of the pancreas, prevents rickets from occurring. A small minority of patients may have hypoprothrombinemia from vitamin K deficiency and may exhibit bleeding. Water-soluble vitamins are absorbed sufficiently well to prevent deficiency syndromes. If hypoprothrombinemia develops, vitamin K should be administered. It is not contained in the usual vitamin mixtures.

Due to impaired digestion and absorption, with perhaps superimposed infection, these patients also tend to be severely anemic. The anemia is usually a hypochromic microcytic type and only rarely megaloblastic.

Although patients without pulmonary infection may eat enough to maintain proper growth, infection is so often present that the usual patient is noticeably retarded in weight and stature, often falling at about the 25 percentile on growth charts. Typically, the abdomen is somewhat protuberant, the muscles are wasted, the arms and legs are spindly, and often the buttocks droop in loose folds. Other patients remain fairly well nourished.

Pulmonary manifestations are initially obstructive in nature and due to viscid mucus alone, but subsequently infection supervenes. Symptoms of respiratory tract involvement may appear during early infancy, or later on. Early manifestations are often wheezy respiration and a hacking cough. Dyspnea, chiefly due to generalized obstructive emphysema, may increase steadily or suddenly, especially if lobar atelectasis, present in some 10 per cent of patients, develops. The cough often becomes paroxysmal in nature, and an erroneous diagnosis of pertussis is frequently made. When the pulmonary manifestations increase in severity, the patient has, in addition to wheezing and paroxysmal coughing, mucopurulent sputum, cyanosis, and in many instances clubbing of fingers and toes.

Although major emphasis has been placed upon the pancreatic lesion, from which the disease receives its name, and upon the resulting digestive disturbances, actually the condition of the patient is more closely related to the lung lesions. Prevention and treatment of pulmonary infection is by far the most important key to management.

Widespread pulmonary involvement of the type described above may lead to two special complications that deserve emphasis: (a) cor pulmonale; (b) respiratory acidosis. Recent reports indicate that cor pulmonale is by no

means uncommon in these patients, at times resulting in cardiac decompensation. The clinical diagnosis is made difficult by (a) the fact that severe generalized emphysema tends to narrow the heart and obscure the expected characteristic configuration of a prominent pulmonary conus; (b) dyspnea already present masks that due to decompensation; (c) emphysema tends in itself to reduce return of blood to the heart, thereby perhaps leading to distention of neck veins; and (d) emphysema displaces the liver downward. Despite inherent difficulties in detection, patients with severe pulmonary involvement should be observed for the onset of decompensation due to cor pulmonale, and digitalis should be given. Once decompensation has occurred, however, experience has shown that the prognosis becomes exceptionally poor.

Owing to interference with air exchange, not only does hypoxia occur but there is retention of carbon dioxide, which increases the carbonic acid level of the plasma. This disturbs the normal 1:20 ratio of carbonic acid to base bicarbonate, and tends to produce a lowered plasma pH and an increased carbon dioxide combining power. In order to extend bicarbonate sufficiently to reestablish the normal 1:20 ratio, chloride is excreted by the kidneys. Such a respiratory acidosis (actually respiratory acidemia with compensatory bicarbonate excess) is difficult to correct because of the intractable interference with air exchange. However, this acidemia must be taken into consideration in management of the patient with marked pulmonary changes.

Another interesting aspect of this disease is the tendency of the patients to have heat exhaustion on less provocation than normal individuals. Andersen first pointed out this fact when she observed that in a series of children with heat exhaustion, about half had cystic fibrosis of the pancreas. In an interesting series of experiments diSant'Agnese and his associates demonstrated that this tendency to heat exhaustion was due to the fact that these children excreted from two to four times the normal amount of sodium and chloride in their sweat and that potassium losses by this route were also excessive. An ingenious "sweat test" has been evolved, and it has even been shown that relatives of fibrocystic patients who do not themselves have overt manifestations of the disease may excrete abnormal quantities of electrolytes in their sweat. Likewise, patients with cystic fibrosis of the pancreas excrete excessive amounts of sodium and chloride in their saliva. Last summer the mother of one of my fibrocystic patients stated that on hot days she often found a salty frost on the temples of her child and had to wipe it away two or three times a day.

Although one may usually suspect the diagnosis strongly from clinical manifestations, laboratory tests are indicated. A large number of such tests have been evolved, not all of which will be discussed here. The two in most general use are (a) studies of the duodenal juice for increased viscosity and decreased or absent pancreatic enzymes, especially trypsin; (b) the stool x-ray film test to determine whether trypsin is present. Other tests, useful from a research standpoint and at times helping settle a controversial diagnosis, include chiefly the vitamin A absorption test, determination of blood amino acids after a gelatin meal, and quantitative determinations of fecal fat and protein nitrogen excretion.

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Duodenal juice in cystic fibrosis of the pancreas has an increased viscosity, and pancreatic enzymes may be at low normal levels, greatly decreased, or absent. It is highly important to realize that initially certain quantities of pancreatic enzymes may be entering the duodenum. This is probably due to the fact that the viscid secretions do not block all the ducts suddenly and simultaneously, and some flow of enzymes may be maintained. As the disease progresses, such patients show progressive decrease in enzyme output. Thus, initially, the diagnosis may have to be made when duodenal enzyme concentrations are at the low normal level, or only slightly decreased.

The stool x-ray film test is based upon the fact that trypsin in the stool will digest the gelatin coating on undeveloped x-ray film, leaving a clear spot. In cystic fibrosis of the pancreas, especially in patients with complete absence of pancreatic enzymes in the bowel, stool dilutions fail to digest the gelatin coating of the x-ray film when a drop of diluted feces is placed on the film and incubated for an hour.

Originally, this test, introduced by Shwachman, was thought to have great validity; patients whose stool dilutions failed to clear the film were thought to have absence of trypsin in the feces, whereas those whose stool dilutions did clear the film were thought to have trypsin present. Later, Johnstone showed that various bacteria in the stools, known as gelatin-liquefying bacteria, or gelatinase-producing bacteria, could cause digestion of the gelatin coating of the film by virtue of the production of this enzyme. However, by diluting the stool 1:100, or even 1:200, the concentration of gelatinase is so small that no digestion of the gelatin coating occurs. Such dilution, however, fails to eliminate the digestive effect of trypsin, if it is present in the stool. Therefore, the stool x-ray film test for cystic fibrosis of the pancreas is now performed with diluted fecal specimens.

Three negative tests (failure to digest the gelatin coating) are regarded as excellent evidence of absence of trypsin. Since administration of penicillin or broad-spectrum antibiotics increases the number of gelatinase-producing bacteria in the bowel, it is advisable to discontinue such antibiotics for several days before the test. Furthermore, it is necessary to discontinue oral substitution therapy with pancreatin for at least three days in advance of the test. If these various points are kept in mind the stool x-ray film test is a good screening procedure, but studies of the duodenal juice are more definitive.

Another modification introduced by Johnstone to differentiate between trypsin and gelatinase as the cause of digestion of the gelatin coating of the film is the use of soybean trypsin inhibitor. If diluted stool digests the coating when the inhibitor is not added, the effect could be due to either trypsin or gelatinase. If the addition of inhibitor results in failure of digestion of the coating, the first specimen did contain trypsin. If digestion still occurs after the use of the trypsin inhibitor, the cause of the digestion is the presence of gelatinase.

The most important objectives of treatment are maintenance of good nutrition and the prevention and treatment of pulmonary infections.

There is considerable difference of opinion regarding the necessity of a special diet for patients with cystic fibrosis of the pancreas. Since in the absence of pulmonary infection a ravenous appetite permits ingestion of sufficient food to allow adequate absorption, even though much fat and protein are lost in the stools, Holt and May do not recommend restriction of fat and have noted no harm from its use in normal amounts. Andersen considers it advisable to restrict fat and believes its use may foster bouts of diarrhea. A high protein intake is advised by all, possibly as much as 6 to 8 Gm. per kilogram per day. Water-miscible polyvitamin preparations in at least double the usual daily allowances should be afforded, and 20,000 international units of vitamin A per day is recommended.

Pancreatic enzymes are usually administered orally to substitute for those lacking in this disease. By their use more adequate digestion of food occurs and fecal wastage is reduced. The stools become more formed and less foul in odor and nutrition improves. Pancreatin granules are employed, being sprinkled upon the food.

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The most important aspect of management of patients with cystic fibrosis of the pancreas is the prevention and treatment of pulmonary infection. Therefore, it is standard practice to employ daily prophylactic antibacterial therapy usually with such broad-spectrum antibiotics as chlortetracycline, oxytetracycline, or tetracycline. Penicillin and sulfonamides may also be employed.

Daily prophylactic broad-spectrum antibiotic therapy has certain inherent hazards, which include: (a) toxic reactions to the drug; (b) sensitization to the drug; (c) resistant organisms gaining dominance and producing fatal infection; and (d) rarely, hypoprothrombinemia due to altered intestinal bacterial flora. Nevertheless, there is greater danger in not using such drugs daily than in employing them.

Recently, the problem of growth of resistant organisms has been emphasized. It has been shown that patients with cystic fibrosis of the pancreas who have been given broad-spectrum antibiotics over a considerable period of time tend to develop infections produced by *Pseudomonas aeruginosa*, or other resistant organisms.

In this regard, three things should be emphasized. First, in order to minimize the overgrowth of resistant organisms, prophylactic therapy should probably be interrupted every four to six weeks for a week or more (if all goes well) in order to permit re-establishment of normal bacterial flora. Second, there should be a rotation of antibiotics, one being used for one course, another for the next, etc. Third, if severe infection occurs during prophylactic therapy, nasopharyngeal and blood cultures should be obtained in order to detect presence of resistant organisms. Sensitivity tests should be performed and antibiotic treatment adjusted accordingly.

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IRON STORAGE DISEASE

In 1935 Sheldon[1] summarized information over the preceding seventy-year period concerning idiopathic hemochromatosis. He emphasized the clinical triad of skin pigmentation, liver disease, and diabetes mellitus, and the pathologic finding of massive deposits of iron and variable fibrosis of the iron-laden tissues. It was suggested that these iron deposits were the consequence of an abnormal tissue avidity for iron derived from heme pigment, and that this disease was best classified as an inborn error of metabolism.

During the following twenty-year period, some 800 cases have been reported, nearly double the number reviewed by Sheldon, and at the same time considerable progress has been made in understanding normal and abnormal iron metabolism. McCance and Widdowson[2] indirectly placed emphasis on iron absorption, when they showed the loss of iron to be restricted. It is now generally conceded that body iron content is regulated more by absorption than by excretion, and that in idiopathic hemochromatosis the controlling mechanism is deranged, resulting in excessive assimilation of iron. The obligatory iron loss in the female as a result of pregnancy, lactation, and menstruation would appear to account for the rarity of idiopathic hemochromatosis in the female.

The nature of the tissue iron deposits in this disease is now clear. These deposits of ferritin and hemosiderin have been shown to be chemically similar to those found in other types of iron loading.[3] By repeatedly bleeding patients it has also been possible to demonstrate that these iron stores are available for heme synthesis.[4] Furthermore, the pattern of distribution of iron in idiopathic hemochromatosis is similar to that produced experimentally in animals through excess iron absorption from diet.[5] Whether iron deposits may produce tissue damage of the type observed in hemochromatosis has not been settled conclusively in the experimental animal. There is more pertinent and convincing evidence in the results of long-continued transfusions in patients with refractory anemia. Here an amount of tissue iron comparable to that found in idiopathic hemochromatosis has been associated with the clinical manifestations of liver damage, skin pigmentation, diabetes, and heart failure, and the findings at necropsy would appear indistinguishable from those seen in idiopathic hemochromatosis. On the basis of evidence that the abnormal deposits of iron in hemochromatosis represent storage of iron and that fibrosis of tissues is a consequence of the extent of these deposits, it seems most appropriate to refer to this condition as *iron storage disease.*

Iron loading through absorption as observed in the Bantu native on an iron intake of 100 to 200 mg. per day, or in other races following prolonged ingestion of medicinal iron, may also produce iron storage disease pathologically indistinguishable from the idiopathic type. There are certain differences which may depend on the rate of accumulation of iron and the route of administration. Thus,

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in idiopathic hemochromatosis an excess absorption of approximately 2 mg. per day leads to organ damage in about forty-five years. In the Bantu native an equivalent amount of iron may be assimilated in twenty years, whereas with repeated transfusions the same amount of iron may be accumulated in four to five years. Iron administered parenterally also differs in its initial distribution, being deposited in the reticulo-endothelial cells and only later moving to the polygonal cells of the liver.

Recent clinical reports have laid emphasis on the frequency of cardiac damage in iron storage disease and warrant its inclusion along with the three other cardinal manifestations. The cardiac complications of heart failure or arrhythmias are particularly prone to develop at an early age.

Diagnosis is dependent on establishing the presence of excess iron and of tissue damage. Useful presumptive tests of the former include evaluation of sternal marrow hemosiderin, serum iron, and urinary hemosiderin. Liver biopsy is the only definitive procedure in evaluating the extent of both iron deposits and tissue damage. Even here difficulty will arise in distinguishing the patients with Laennec's cirrhosis plus excessive tissue iron from true iron storage disease.

Bleeding has proved to be a feasible means of removing the excessive iron deposits in idiopathic hemochromatosis.[6] This procedure takes advantage of the normal compensation of the body to blood loss; that is, the mobilization of storage iron and its incorporation into the circulatory red cell mass. The ease with which patients can replace blood loss is good indication of the importance of iron in blood regeneration following hemorrhage. While much of the tissue damage might be assumed to be permanently established in idiopathic hemochromatosis, phlebotomy treatment has been reported to produce improvement in manifestations of liver disease, diabetes, and heart failure.

The likely value of this more specific therapeutic approach shifts attention to early diagnosis before excessive tissue damage has become established. Of interest in this connection is the evidence that iron excess may be demonstrated in one-fourth to one-third of relatives of patients with this disease.[7]

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THE ENLARGING ROLE OF THE GENERAL PRACTITIONER IN TUBERCULOSIS THERAPY

The responsibility for the long-term care of the patient with pulmonary tuberculosis is in the process of being transferred from the specialist in the tuberculosis sanatorium to the general practitioner. This transfer is not likely to be orderly for it was not planned. On the contrary, the transfer is unpremeditated and simply represents an inevitable consequence of the technologic developments of the past decade.

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One consequence of these developments is a situation whereby the practitioner of today can supply to his tuberculosis patient in the home considerably more powerful antituberculous influences than were available in the best-equipped sanatoriums ten years ago. Another consequence is the fact that effective therapy has led to a considerable enlargement of that group of patients whose tuberculosis presents problems in management resembling those of the noninfectious chronic disease states. Tuberculosis of this type presents essentially the same problems as occur with persons with a tendency to develop peptic ulcer. The patient is customarily well and fully active, but on occasion every few years or so he experiences a minor flare-up of his tuberculosis. Indeed, in large measure this type of problem almost certainly represents the prototype of "the tuberculosis problem" of the future. Such situations should be within the proper province of the well-informed general practitioner and presumably he will be asked more and more to assume responsibility for them.

It should be recognized that this transfer for the major management of a *disease* is relatively unprecedented. The practitioner quite expects that the discovery of the first effective *treatment* for a disease may make it suddenly necessary for him to increase his general fund of knowledge about that disease. This was the case, for example, with the discovery of insulin for diabetes or liver extract for addisonian anemia. In most such circumstances, however, the practitioner's knowledge and that of the "experts" are essentially equal and all go on to learn the new facts together. What the practitioner does not expect, however, is that he should find himself assuming the responsibility for a disease with which he has had little experience and one, moreover, for which highly complicated methods of treatment have been developed over a period of some years.

The current situation may be characterized by an only slightly exaggerated example. Let it be imagined that heart disease and its management with digitalis, acetazoleamide (Diamox), mercurial diuretics, anion exchange resins, and anticoagulants had for years been the province of the staffs of remotely situated sanatoriums. Let it then further be imagined that technologic developments in this field began and continued at such an accelerating rate that

the practitioner, hitherto only broadly aware of the problems of heart disease or its treatment, now found himself largely responsible for both.

If this example seems unduly exaggerated, let it be recalled that the current generation of general practitioners in the United States have had virtually no experience as medical students, as residents, or in their subsequent careers, with the day-to-day and month-to-month decisions involved in the treatment of pulmonary tuberculosis. The situation is no different for the current generation of accredited specialists in internal medicine. As a consequence we now have a largely untrained group of men in the process of receiving the responsibility for the daily management of one of the major diseases. This is occurring, moreover, at the very time when there are substantial differences of opinion on the specific details of treatment among those most experienced with the disease.

I believe that the force of the technologic developments in both the surgical and the medical treatment of tuberculosis are making this transfer so inevitable that it serves no useful purpose to debate whether its ultimate effects will be good or bad. In the short run, such an unorganized transfer of medical responsibility has within it the potentialities for considerable harm for all concerned. In the long run, it will probably prove to be a good thing.

The compelling question is how the transfer can be accomplished. In more precise terms, how can it be accomplished with the least harm to the patients, their families, and the general public? For it must be remembered that all of these groups are being most capably served today by the tuberculosis control methods developed and maintained through the years by such groups as the National Tuberculosis Association, various governmental agencies, and the sanatorium physicians themselves.

What is the general practitioner to do, faced as he is with this generally unsought and wholly new area of responsibility? The first step must be the recognition by both the practitioner and the chest specialist that there *is* a problem and that its proper solution will require a new and considerable expenditure of joint labor by both.

Earlier in this editorial it was stated that the practitioner can deliver in the home today a considerably more powerful antituberculous attack than was available in the sanatorium ten years ago. This represents a true description of a broad general phenomenon. In terms of an individual patient, however, this statement may well represent only a part of the truth. For, what the practitioner can deliver in the *home* today is by no means necessarily the best treatment *available today* for a particular patient with pulmonary tuberculosis. On the contrary, a treatment for tuberculosis which might be extraordinarily powerful when considered in general terms might represent precisely the wrong thing to apply in the home, or in the hospital, for that matter, in the case of a particular patient.

The possibilities for widespread harm by the injudicious application of powerful antituberculous chemotherapy today, recalls vivid memories for those who were engaged in the treatment of syphilis only a few decades ago. At that time every physician in America knew that "606" or some of its derivatives

were "good" for syphilis. Armed with that knowledge, and frequently with little else, many physicians believed themselves to be entirely competent to treat all cases of syphilis and, indeed, they did so. As a consequence, it is safe to state that the great majority of patients who received treatment for syphilis in the prepenicillin era were incorrectly treated. Their treatment was either grossly inadequate or they were grossly overtreated.

The ironic tragedy of this situation was the fact that the physicians involved really were "competent" to treat syphilis in the sense that they could very easily have become so with a very small educational effort. In actuality, the basic principles involved in the treatment of syphilis and their proper application were not at all complicated. Nevertheless, the situation continued to endure for approximately twenty-five years despite the efforts of a few individuals. Indeed, it was not until the thirties that a truly widespread educational effort for both the physicians and the laity was launched.

The educational effort represented a series of closely coordinated but independent activities. They were originated and conducted by public-spirited physicians, university clinics, voluntary health organizations such as the American Social Hygiene Association, and by Federal, state, and local departments of health. The men engaged in this effort faced difficulties which were formidable. Not the least of their difficulties was the fact that the very name of the disease toward which the educational program was directed was itself not then a "mentionable" word in polite society. Nevertheless, this educational movement enjoyed a very large measure of success and was almost wholly responsible for the vastly improved situation with respect to the treatment of syphilis in the United States which existed by the time we entered World War II.

The problems faced by the practitioner today with respect to his participation in the treatment of tuberculosis are not identical with the corresponding problems with respect to syphilis in the 1930's. Nevertheless, there are many similarities. In both situations the cardinal fact is that the practitioner, through no fault of his own, lacks (or lacked) certain important information concerning the disease and practical experience in its treatment. In both situations, however, the necessary knowledge is not at all difficult to master by any one equipped to practice medicine today. In the case of syphilis, the practitioner, if he chose, could avoid the effort required to obtain this necessary knowledge. The relatively few cases he might encounter could usually be just as well referred elsewhere. With tuberculosis, however, it is probable that the practitioner will find it inadvisable simply to evade the issue. On the contrary, he will probably be anxious to assume this new responsibility provided that he can reassure himself that some aspects of the subject can be made to lie within his own field of competence.

The central problem, therefore, would seem to be in the *delivery* of sufficient theoretical and practical knowledge to the practicing physician to equip him to fulfill a proper role in the treatment of tuberculosis. As in this major respect the problem seems identical with that presented by syphilis in the 1930's, it would seem the course of wisdom to attempt to attack it in the same way, namely, by a widespread educational effort for the benefit of the practitioner.

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Superb facilities now exist which might conceivably be expanded to take on the additional load which a physician-oriented educational effort would involve. It must be recognized, however, that the extension of these facilities to embrace such an educational program would immediately present real problems for both the governmental and nongovernmental agencies concerned.

For example, in the voluntary health movement, the National Tuberculosis Association with its Christmas Seal funds has led the way in widespread health education programs for more than fifty years. Included in its program, moreover, are substantial allocations for basic research and for the training of physicians at both the undergraduate and postgraduate levels.

The propriety of a voluntary health organization participating in such activities is quite generally accepted. What is not so clear, however, is just how a voluntary health organization could arrange to deal directly with individual practitioners on a matter of scientific education. Moreover, the same situation obtains for the tuberculosis control divisions of the various governmental agencies.

The phrase "deal directly with individual practitioners" is used advisedly. At the present time both the voluntary and the governmental health groups can and do arrange for symposiums and lecture courses. Admirable as these may be, however, they are but a pallid imitation of the process of clinical education. The way in which a physician really learns something of a clinical nature is by facing a question raised in terms of a patient, preferably a patient for whom he shares some measure of responsibility. It would be highly desirable, therefore, in attempting a widespread educational program suited to the present problem, to revive or create some formula by which the enormous benefits of the physician-consultant teaching relationship could be maintained.

Such a formula might be found, for example, in having consultants or consultant teams travel to a particular community and make "teaching rounds," so to speak, with individual practitioners *and their own patients*. In a two-day period, four or five such "rounds" could be held in a particular community provided that reasonable prior attention were given to the details of an appointment schedule. Whether the several practitioners involved would "sit in" on each others' consultations or whether the consultations would be "private" would depend on the immediate circumstances, and the matter could be handled either way. The travel expenses and perhaps a modest honorarium for the consultant-teachers could be provided by health organizations and medical societies, and the community arrangements could be made by the local medical society.

It might be objected that it is economically impracticable to transport and maintain one or two well-recognized experts for a two- or three-day period for an audience composed of only five or six practitioners. In answer, it can be stated that this audience, almost without exception, would have a real interest in the matter and, what is more, it would be in a position to gratify that interest. Assurance of a comparable state of active receptivity in five or six of the audience would seem quite a sufficient reward to any but the most self-deluding of our visiting medical lecturers on the customarily rainy winter evening.

Regardless of whatever formulas might prove workable, it seems of considerable importance that there be a joint effort to increase the practitioner's general knowledge and practical experience with pulmonary tuberculosis as rapidly as possible. At the outset, moreover, the primary emphasis in such an educational effort should be on a few basic principles. The principles are those which would permit the general practitioner to identify those situations which require immediate expert consultation and to distinguish them from the situations which he is already capable of handling on his own. These principles, in themselves, should not be difficult to grasp by any physician practicing medicine today. Nevertheless, the actual arrangements by which presentation of these principles and some practical experience in their application can be provided for the practitioner will involve a considerable effort for all concerned.

Finally, in making his part of the effort the practitioner may find himself confused on a few particulars, notably, to what extent chemotherapy modifies the necessity for bed rest. On this question, if confusion arises, he can derive whatever solace he can from the fact that in a very real sense he and the experts are all in it together.

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Book Reviews

ANTIBIOTISM AND IMMUNITY MEDICINE OF TO-MORROW: By Alexander Komis, M.D. Pp. 72. Bristol, England, 1954, John Wright & Sons, Ltd. Price $2.75.

Dr. Komis, Director of the Scientific Department of the Institute of Fermented Vaccines in Athens, Greece, has written a monograph which this reviewer found fascinating but fantastic. For many years, the author has experimented with methods of producing vaccines and antigens for immunization, using a technique that involves growing bacteria in media containing yeast and carbohydrates unde. conditions favoring fermentation and alcohol production. Basically, this monograph argues for the use of these techniques of vaccine preparation because they represent the only hope for rational prevention and treatment of infectious disease.

Present-day antibiotics and emphasis upon their use in therapy are regarded by Dr. Komis as one of the greatest tragedies in history. For example, he states (pp. 7-8): "They do not radically cure diseases, for relapses very often appear after treatment by them. They create resistant strains of microbes. . . . New clinical forms of disease appear resistant to all treatment. . . . A serious epidemiological problem of extension of the actual diseases and the creation of new ones has appeared. . . . Even the creators of antibiotics are obliged by the above distressing facts, albeit a little late, to take refuge in the true medicine, in the study of *immunity*."

On pp. 27-28: "We now go forward to 1939, which was disastrous both to medicine and to humanity, for during this year antibiotism was definitely separated from immunity and Medicine therefore was pushed back to the empiricism of the past century and humanity was deprived of the redemption of its disease by the natural means of immunology proved already from many years. One can even consider the second day of September, 1939, when the Third International Congress of Microbiology began its work in New York, as a kind of ill-omened day. From that date Medicine almost completely removed the subject of immunity from its field and embraced the empiricism of to-day's antibiotism. . . . Dubos presented the conclusions of his researches which had resulted in the preparation of the first antibiotic Tyrothricin, from *Bacillus brevis*. By a misfortune for Medicine Welsch at the same time connunicated . . . a paper . . . concerned . . . specifically with the isolation from Actinomyces . . . of actinomycetin. . . . The discissuon upon this matter was generalized and both Fleming and Waksman took part . . . the latter even supported the belief that . . . soils . . . could offer us more important substances than those . . . in Dubos' tyrothricin."

On pp. 29-30: "For a long time, however, there has been a certain scepticism about the antibiotism of today, a prelude to its probable decadence in the future. More relapses and complications occur today as a result of the use of the antibiotics. By these, diseases are only suspended, they are not definitely cured. . . . To-day antibiotics suspend the multiplication . . . of microbes, but do not immunize. . . . The lack of natural immunity and principally of acquired immunity is the main and only reason for the incomplete and unstable curative action of antibiotics to-day."

On p. 40, after a description of fermented vaccines (the production of "antibiotized vaccines"): "It is superfluous to report other researches and more details. . . . What has been put forward here is more than enough to prove that Hellenic medicine, from 1928 onwards, has erected a brilliant building of immunity on the solid base of antibiotism, and especially of potent antibiotism as realized by alcoholic fermentation. It is only this association . . . that leads medicine to the definite solution of the problem of treatment and prevention of disease."

Finally, on p. 62: "Progress in our era brought about by the discovery of the antibiotics is none other than a return to the empiricism of the past century and that which reigned in medicine before the time of Hippocrates. The collossal(sic) building of immunity constitutes the only true medicine and embraces the radical treatment of disease as well as the certain prevention of it. Its perfection by microbial antibiotism and antagonism will bring us the progress expected of medicine for centuries."

Although it can be said that there is a certain intrinsic interest in such extreme views, there is not enough of scientific moment or of practical applicability in this monograph to lead one to recommend its purchase by the individual. It should be on deposit in large medical libraries.

IVAN L. BENNETT, JR.

APHASIA REHABILITATION. By Martha L. Taylor, M.A., and Morton Marks, M.D. New York, 1955, Institute of Physical Medicine and Rehabilitation. Price $3.00.

This is a very much simplified workbook, designed for use by an untrained person with an adult who suffered an expressive aphasia. There is no pagination, largely for the reason that most of the pages are designed for removal and active use as individual work-picture combinations. A group of 100 nouns was selected; each word is printed in large type and each can be cut out and mounted on the back of the matching picture. This sort of word-picture drill is fundamental in retraining aphasics, and provides a good basis for the all-sensory-motor rehabilitative scheme that most therapists employ.

The first few pages include some introductory remarks about aphasia and a set of instructions for an untrained person. This is a valuable contribution, for it should help the family of the affected person to gain considerable insight into his communicative problems and needs. There follows an outline of nine steps in retraining procedures; these are specific directions and goals, relative to the use of the 100 word-picture combinations, that should be clear to anybody who can read.

This manual fills a need and should help materially to bridge the gap between obscure cortical lesions and the recapturable function in language and speech of the aphasic person.

WILLIAM G. HARDY

DIRECTORY OF FACILITIES FOR CARE OF PATIENTS WITH RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE; BIBLIOGRAPHY LISTS ON RHEUMATIC FEVER; and LIST OF PUBLICATIONS ON RHEUMATIC FEVER FOR LAY PERSONS are all available on request from the Helen Hay Whitney Foundation, 525 East 68th Street, Room F-231, New York 21, N. Y.

The directory, revised in April, 1955, lists the facilities available nationally as to hospitals, convalescent homes, etc., for the care of patients, especially children, with rheumatic fever, and should be of material value to physicians who wish to provide specialized care for such children.

The bibliography lists several thousand titles on the following topics, relating to rheumatic fever and to rheumatic heart disease, subdivided in the following categories:

1. Camping for Handicapped Children.
2. Community Rheumatic Fever Programs.
3. Convalescent Care.
4. Education of Exceptional Children.
5. Epidemiology of Rheumatic Fever.
6. Incidence of Rheumatic Fever.
7. Occupational and Recreational Therapy.
8. Prevalence of Rheumatic Heart Disease.
9. Prevention of Rheumatic Fever.
10. Recurrence of Rheumatic Fever.
11. RF (and Cardiac) Clinics.
12. Vocational Guidance and Rehabilitation.

The bibliography is not complete, but, nevertheless, includes most of the important recent publications. It is available, together with the Directory of Facilities, and the List of Lay Publications, free of charge on inquiry to the Helen Hay Whitney Foundation.

The list of publications for lay persons is designed to aid the physician in selecting reading material suitable for "educating" the families of his rheumatic fever patients.

Claire Allen

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